

# In the United States Court of Federal Claims

## OFFICE OF SPECIAL MASTERS

Filed: March 29, 2019

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JORDIA NUNEZ and JOHN DIAZ,  
as legal representatives of J.J.D.,  
an infant, deceased,

Petitioners,

v.

SECRETARY OF HEALTH  
AND HUMAN SERVICES,

Respondent.

\* \* \* \* \*

\* No. 14-863V  
\*  
\* Special Master Sanders  
\*  
\* Hepatitis B (“HBV”) Vaccine; Rotavirus  
\* Vaccine; Diphtheria-Tetanus-acellular  
\* Pertussis (“DTaP”) Vaccine; Haemophilus  
\* Influenza Type B (“HiB”) Vaccine;  
\* Inactivated Polio Vaccine (“IPV”);  
\* Pneumococcal Conjugate Vaccine; Sudden  
\* Infant Death Syndrome (“SIDS”); *Althen*  
\* Causation

*Sylvia Chin-Caplan*, Law Office of Sylvia Chin-Caplan, Boston, MA, for Petitioners.  
*Adriana R. Teitel*, United States Department of Justice, Washington, D.C., for Respondent.

### **DECISION ON ENTITLEMENT**<sup>1</sup>

On September 17, 2014, Jordia Nunez and John Diaz (“Petitioners”), as legal representatives of J.J.D. (“J.J.”),<sup>2</sup> a deceased infant, filed a petition pursuant to the National Vaccine Injury Compensation Program.<sup>3</sup> Petitioners alleged that the death of their minor son, J.J., was caused by “adverse effects” of hepatitis B virus (“HBV”); rotavirus; Diphtheria-Tetanus-acellular Pertussis (“DTaP”); haemophilus influenza type B (“HiB”); inactivated polio (“IPV”); and pneumococcal conjugate vaccines that he received on November 14, 2012. Pet. at 1, ECF No. 1; Amended Pet. at 1, ECF No. 21-1.

After carefully analyzing and weighing all the evidence and testimony presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioners have

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<sup>1</sup> This decision shall be posted on the United States Court of Federal Claims’ website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

<sup>2</sup> J.J.D. was referred to as “J.J.” throughout the hearing, despite the caption. J.J. will be used throughout the opinion. Tr. at 10:15.

<sup>3</sup> The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. (hereinafter “Vaccine Act,” “the Act,” or “the Program”).

not met their legal burden. Petitioners have not provided preponderant evidence that the vaccinations J.J. received on November 14, 2014, can cause SIDS generally, or that one or more of them caused J.J. to succumb to SIDS. Accordingly, Petitioners are not entitled to compensation.

## **I. Procedural History**

This case was originally assigned to Special Master Hamilton-Fieldman. *See* ECF No. 4. Petitioners filed eleven exhibits consisting of medical records and affidavits. Pet'rs' Exs. 1–11; ECF No. 6–1–6.11. On February 3, 2015, Respondent filed his Rule 4(c) Report. ECF No. 11. Respondent argued that Petitioners' claim "lack[ed] any medical corroboration" and that Petitioners had "not proffered any mechanism of injury to explain how [J.J.'s] death was vaccine-related." *Id.* at 5. Respondent also noted that "[n]o treating physician ha[d] ascribed [J.J.'s] death as being related to any of the vaccinations he received on November 14, 2012." *Id.*

On June 19, 2015, Petitioners filed an amended petition, substituting initials for J.J.'s name throughout the document and adding language alleging that J.J.'s death was "a result of the adverse effects" of the vaccines he received. Amended Pet. at 1. The same day, Petitioners filed an expert report authored by Dr. Douglas Miller. Pet'rs' Ex. 12, ECF No. 21-2.

On November 19, 2015, Respondent filed two responsive expert reports, authored by Dr. Christine McCusker and Dr. Rebecca Folkerth. Resp't's Exs. A, C, ECF Nos. 37-1, 41-1. Thereafter, Petitioners filed a supplemental expert report authored by Dr. Miller on January 19, 2016. Pet'rs' Ex. 37, ECF No. 44-1. Respondent filed supplemental responsive expert reports authored by Dr. McCusker and Dr. Folkerth on April 11, 2016, and April 14, 2016, respectively. Resp't's Exs. E, F, ECF Nos. 51-1, 56-1.

At a status conference held on May 10, 2016, the parties agreed to proceed to an entitlement hearing. Order, ECF No. 58. Another status conference was held on October 18, 2016, and the parties discussed the case in light of Special Master Hamilton-Fieldman's August 29, 2016 decision denying entitlement in a similar case, *Jewell v. Sec'y of Health and Human Servs.*, No. 11-138V, 2016 WL 5404165 (Fed. Cl. Spec. Mstr. Aug. 29, 2015). Order, ECF No. 59. Ultimately, Petitioners admitted that their case bore many similarities to *Jewell*, but they requested to proceed to a hearing. *See id.*; Pet'rs' Stat. Rept., ECF No. 65.

The case was reassigned to the undersigned on January 10, 2017. *See* ECF Nos. 66–67. At a status conference held on February 16, 2017, the parties discussed the case and the features which Petitioners felt distinguished their case from *Jewell*. *See* Order, ECF No. 69. Petitioners again requested that they and their expert be afforded an opportunity to testify at an entitlement hearing. *Id.* Thereafter, Petitioners filed a second supplemental expert report authored by Dr. Miller and a second affidavit authored by Petitioner Jordia Nunez ("Ms. Nunez"). Pet'rs' Exs. 38–39, ECF No. 71-1, 71-2.

An entitlement hearing was held in Washington, D.C., on February 22 and 23, 2018. The parties timely filed post-hearing briefs. ECF Nos. 103, 106, 110. This matter is now ripe for a decision.

## II. Factual Background

### A. Medical Records

Ms. Nunez was in her early twenties when she became pregnant with twins in 2012. Pet'rs' Ex. 5 at 24 (filed on compact disk; ECF No. 6). Ms. Nunez had previously given birth to a baby girl in 2008 and had experienced preeclampsia and mild hypertension with that pregnancy. *Id.* The 2012 pregnancy was considered high risk due to Ms. Nunez's history and it being a twin gestation, but an early workup for preeclampsia and hypertension was negative. *Id.* at 66, 82. Ms. Nunez attended several prenatal appointments between March and July 2012. *See id.* at 23–99. On July 10, 2012, Ms. Nunez was transported to Bronx Lebanon Hospital in pre-term labor. Pet'rs' Ex. 2 at 5 (filed on compact disk; ECF No. 6). Ms. Nunez naturally delivered twins on July 11, 2012. Pet'rs' Ex. 6 at 6 (filed on compact disk; ECF No. 6). J.J. and his twin sister were born at approximately twenty-nine weeks and two days' gestation. *Id.* at 8; Pet'rs' Ex. 2 at 58. J.J.'s Apgar scores<sup>4</sup> were seven and eight at one minute and five minutes, respectively. Pet'rs' Ex. 6 at 6. The twins were transferred to the neonatal intensive care unit ("NICU") after birth due to their prematurity. *Id.* at 6, 27; Pet'rs' Ex. 2 at 58. Ms. Nunez was discharged from the hospital on July 13, 2012. Pet'rs' Ex. 2 at 58.

J.J. had episodes of respiratory distress upon admission to the NICU, and he received nasal continuous positive airway pressure ("NCPAP") from July 11 through July 15, 2012. Pet'rs' Ex. 6 at 29, 34, 36, 38, 40, 898–99. He remained in the NICU until August 31, 2012, when he was discharged home in stable condition. *Id.* at 901.

On September 13, 2012, J.J. was seen by Dr. Yves Verna for his two-month well-baby examination. Pet'rs' Ex. 7 at 1–3 (filed on compact disk; ECF No. 6). Dr. Verna noted that J.J. was taking vitamin supplements and that he was being breastfed approximately every twelve hours, supplemented with cow's milk formula as needed. *Id.* at 1. Dr. Verna wrote that J.J. was "[w]ell-appearing, alert, well hydrated, and active" and that he was "[n]ot acutely ill." *Id.* She noted the following about J.J.'s growth and development: "Vocalizes, attentive to voices, has a social smile, the gaze follows past the midline, lifts the head and chest off a surface, the head is steady in an upright position, and the hands are open 50% of the time." *Id.* at 2. J.J. received rotavirus, DTaP, HiB, IPV, and pneumococcal conjugate vaccines during the visit. *Id.* at 3. J.J.'s parents were instructed to give him Tylenol every four hours for 48 hours after vaccination. *Id.* at 2.

On November 14, 2012, J.J. was brought to Dr. Verna for his four-month well-baby examination. Pet'rs' Ex. 7 at 3–5. Dr. Verna documented that J.J. had "[n]o fever," "[n]o cough," his "[a]ppetite [was] not decreased[,]" and he had "[n]o difficulty sucking." *Id.* at 3. She also documented that there were "[n]o parental concerns about hearing[, vision[, or] behavior." *Id.* J.J. weighed 11 lbs. and measured 22.75 inches long with a head circumference of 39.5 cm. *Id.* Those measurements put him at the low end of the normal range for weight and slightly under the

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<sup>4</sup> An Apgar score is "a numerical expression of the condition of a newborn infant . . . being the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color." *Dorland's Illustrated Medical Dictionary* 1682 (32nd ed. 2012) [hereinafter "*Dorland's*"]. Between seven and ten is considered "[n]ormal [r]ange." *See* Pet'rs' Ex. 7 at 2.

normal range for body length and head circumference. *Id.* Dr. Verna wrote that J.J. was “[w]ell-appearing, alert, well hydrated, and active.” *Id.* She noted the following about J.J.’s growth and development: “Turns toward voices, visual track 180 degrees, laughs, no head lag when pulled to sitting position, brings hands together, and reaches for objects.” *Id.* at 4. The physical examination portion of the note reflects no abnormalities, including “[n]o nasal discharge seen.” *Id.* at 3. J.J. received HBV, rotavirus, DTaP, HiB, IPV, and pneumococcal conjugate vaccines during the visit. *Id.* at 5. The note reflects that the vaccines were administered between 5:40 p.m. and 6:24 p.m. that evening. *Id.* at 4–5. J.J.’s parents were instructed to give him Tylenol every four hours for 48 hours after vaccination. *Id.* at 4.

The next morning, on November 15, 2012, a 911 call was made from Petitioners’ residence at around 9:49 a.m. Pet’rs’ Ex. 8 at 1 (filed on compact disk; ECF No. 6). The caller described J.J. and stated: “He’s not breathing.” *Id.* An ambulance was dispatched and arrived at Petitioners’ home at 9:53 a.m. *Id.* EMS crew members evaluated J.J. and found him to be unresponsive, with non-reactive pupils and absent lung sounds. *Id.* at 3. The crew members documented that J.J.’s skin color was either cyanotic<sup>5</sup> or normal, and his skin temperature and condition were marked as normal. *Id.* Crew members found no injuries on physical examination. *Id.* At both 9:55 a.m. and 10:00 a.m., J.J. was found to have no pulse or respiration. *Id.* In the ambulance, J.J. was treated with a bag valve mask, oral/nasal airway support, CPR, and oxygen therapy. *Id.* Petitioners reported to the EMS crew members that J.J. was last awake at 11:00 p.m. the night before. *Id.* The ambulance left Petitioners’ home at 9:57 a.m. and arrived at the nearest hospital at 10:01 a.m. *Id.* at 1. J.J. was pronounced dead at the hospital at 10:23 a.m. Pet’rs’ Ex. 9 at 12 (filed on compact disk; ECF No. 6); Pet’rs’ Ex. 6 at 1.

The attending physician upon arrival at the hospital was Dr. Ye Aung. He and a resident authored a note which includes a timeline of events provided by Petitioners. Pet’rs’ Ex. 9 at 15–19. The note reflects that J.J. had received vaccinations in the previous evening and had been given Tylenol. *Id.* at 16. Petitioners reported that J.J. “was a bit cranky,” that he was fed formula around 9:30 p.m., and that he was put to bed at around 11:00 p.m. *Id.* Petitioners stated that the next morning, Ms. Nunez awoke at around 8:30 a.m., found J.J. and his twin sister sleeping, and took the older sister to school. *Id.* Mr. Diaz brought J.J.’s twin sister to the living room at approximately 9:00 a.m. because she had awakened and J.J. remained sleeping. *Id.* Ms. Nunez returned home at around 9:30 a.m. and checked on J.J. She saw that “his face [was] all blue and unresponsive[.]” *Id.* Ms. Nunez “carried [J.J.] to the living room, called 911, and started a cardiopulmonary resuscitation on him.” *Id.*

The note also includes a timeline that Petitioners provided to a social worker at the hospital. Pet’rs’ Ex. 9 at 15. According to the note, Petitioners relayed that Ms. Nunez last checked on J.J. and his twin sister at 11:00 p.m. the previous evening. *Id.* J.J. and his twin sister “slept thr[ough] the night as always[.]” *Id.* The next morning, Ms. Nunez took her oldest daughter to school after checking on the twins. *Id.* Mr. Diaz relayed that J.J.’s twin “started crying [and] he hurried up to pick her up so she would not wake” J.J., who “appeared to be asleep[.]” *Id.* When Ms. Nunez returned home, she observed Mr. Diaz and J.J.’s twin sleeping together, and she checked on J.J. *Id.* At that point, Ms. Nunez “noticed [J.J.] was not breathing and screamed” for Mr. Diaz. *Id.*

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<sup>5</sup> Cyanosis is “a bluish discoloration, especially of the skin and mucous membranes due to excessive concentration of deoxyhemoglobin in the blood.” *Dorland’s* at 452.

Ms. Nunez “tried blowing in [J.J.’s] mouth[,]” and Mr. Diaz “called the police.” *Id.* The note reflects that the social worker contacted the authorities, but that child services “decline[d] to [a]ccept the case[,] [c]iting [the] M.D. rul[ing]” that the cause of death was SIDS. *Id.*

An autopsy was performed on November 16, 2012, by Dr. James Gill. Pet’rs’ Ex. 10 (filed on compact disk; ECF No. 6). Dr. Gill’s report reflects that J.J. was “a well-developed, well-nourished, average-framed, 23[-inch-long], 14-pound” boy, with no evidence of recent injury. *Id.* at 5. The head was “turned to the right on presentation.” *Id.* Dr. Gill noted bandages on the thighs, commenting that there were “recent vaccinations.” *Id.* Dr. Gill indicated that the myocardium, lungs, liver, kidneys, spleen, intestines, stomach, esophagus, laryngeal wall, thyroid gland, and thymus gland were unremarkable, although petechiae<sup>6</sup> were noted on the thymus gland.<sup>7</sup> *Id.* at 1. He noted a “[f]ocal epicardial hemorrhage” in the heart. *Id.* He also noted “[p]ancreas with autolysis” and “[a]drenal glands with medullary congestion.” *Id.* A nasopharyngeal swab was tested, but no influenza viruses were detected. *Id.* at 2.

Under a section of the report entitled “Final Diagnoses,” Dr. Gill wrote the following:

- I. SUDDEN UNEXPECTED DEATH IN INFANT.
  - A. HISTORY OF PREMATUREITY (26 [sic] WEEKS).
  - B. RECENT UPPER RESPIRATORY INFECTION.
  - C. RECENT IMMUNIZATIONS.
  - D. ONE OF A TWIN GESTATION.
  - E. CO-SLEEPING WITH TWIN IN CRIB.
  - F. BLOOD AND CSF CULTURES: NEGATIVE.
  - G. INFLUENZA STUDIES: NEGATIVE.
  - H. TOXICOLOGY POSITIVE FOR ACETAMINOPHEN.
  - I. METABOLIC STUDIES: NEGATIVE.

*Id.* at 3. Dr. Gill ruled that the “cause of death” was “Sudden Infant Death Syndrome” and the “manner of death” was “natural.” *Id.*

An examination of the brain was performed by Dr. Hernando Mena on November 27, 2012. Pet’rs’ Ex. 10 at 10. The brain weighed 618 grams. *Id.* Dr. Mena wrote that microscopic examination revealed “reactive [sic] astrocytes<sup>8</sup> within the region of the raphe nucleus in the midbrain and pons, and medullary inferior olivary nuclei. The intracranial dura reveals formation of a subdural fibrovascular membrane with few hemosiderin-laden macrophages.” *Id.* The report reflects two diagnoses: (1) “subdural hemorrhage, organized, cerebral convexities;” and (2) “[g]lissosis,<sup>9</sup> brain stem nuclei.” *Id.*

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<sup>6</sup> A petechia is “a pinpoint, nonraised, perfectly-round, purplish red spot caused by intradermal or submucous hemorrhage.” *Dorland’s* at 1422.

<sup>7</sup> The thymus is a lymphoid organ. *Dorland’s* at 1925. It is the site where T lymphocytes are produced. *Id.*

<sup>8</sup> Astrocytes, also known collectively as astroglia, are neuroglial cells of ectodermal origin. *Dorland’s* at 169–70. They “appear to play a role in myelin formation, transport of material to neurons, and maintenance of the ionic environment of neurons.” *Id.* at 1265.

<sup>9</sup> Gliosis is “an excess of astroglia in damaged areas of the central nervous system.” *Dorland’s* at 784.

The accuracy of the medical records is not in dispute in the case. Both parties agree on the date and circumstances surrounding J.J.'s vaccinations as represented in the medical records. Additionally, J.J.'s medical history is not disputed by either party, although different conclusions are drawn from symptoms and test results within the record. Both parties also agree that J.J.'s cause of death was SIDS and that all the information noted in the autopsy report is accurate; however, the significance of any objective finding may be in dispute.

## **B. Affidavits**

Ms. Nunez filed two affidavits and Mr. Diaz filed one affidavit. Pet'rs' Exs. 3–4, 39 (filed on compact disk; ECF No. 6), ECF No. 71-2. The affidavits were consistent with the medical records detailing Ms. Nunez's pregnancy and the twins' medical histories. Ms. Nunez wrote that J.J. "had respiratory problems due to lung immaturity and was placed on a CPAP machine[, and that h]e was also placed on antibiotics and in photo therapy for jaundice." Pet'rs' Ex. 3 at 2; *see also* Pet'rs' Ex. 4 at 2. Both parents also wrote that "[a]ll testing that was done on [J.J.] came back normal" and he "was the healthier, stronger of the two" twins. *Id.* They wrote that J.J. was discharged from the NICU on August 31, 2012, while his twin remained in the NICU until September 7, 2012. *Id.* Ms. Nunez wrote that the twins "slept together at opposite ends of their crib. When they were put to bed at night, they each had a light blanket that [she] tucked around their waist. There were no pillows in their crib." Pet'rs' Ex. 39 at 1.

Ms. Nunez and Mr. Diaz both wrote that J.J. was examined and found to be "a healthy baby" at his first well-baby visit on September 13, 2012. Pet'rs' Ex. 3 at 2–3; Pet'rs' Ex. 4 at 2. They described a call to the pediatrician in October 2012 because J.J. "had a stuffy nose." Pet'rs' Ex. 3 at 3; Pet'rs' Ex. 4 at 2. They wrote that Ms. Nunez "was told to use saline." *Id.* After that, Ms. Nunez wrote that J.J. "continued to thrive." Pet'rs' Ex. 3 at 3. Mr. Diaz wrote that J.J. "was growing and getting stronger." Pet'rs' Ex. 4 at 2.

Both parents wrote that J.J. had his four-month visit with Dr. Verna on November 14, 2012, at approximately 7:00 p.m. Pet'rs' Ex. 3 at 3; Pet'rs' Ex. 4 at 2. Both also wrote that J.J. and his twin sister "had runny noses and productive coughs" on that date. *Id.* Ms. Nunez wrote that Dr. Verna "did not perform a physical examination" on either twin and that "neither their ears [n]or chests were checked." Pet'rs' Ex. 3 at 3. Mr. Diaz wrote that Ms. Nunez "pointed out [the symptoms of runny nose and cough] to the doctor." Pet'rs' Ex. 4 at 2. The parents wrote that Dr. Verna weighed, measured, and administered vaccinations to the twins. Pet'rs' Ex. 3 at 3; Pet'rs' Ex. 4 at 2.

Both parents wrote that they returned home at approximately 8:30 p.m. that evening. Pet'rs' Ex. 3 at 3; Pet'rs' Ex. 4 at 3. J.J. was fed and given Tylenol because he "was fussy and his nose was still running." *Id.* Ms. Nunez added that J.J. "did not have any fever." Pet'rs' Ex. 3 at 3; *see also* Pet'rs' Ex. 39 at 1. The parents wrote that J.J. was placed in a vibrating chair and fell asleep at around 10:30 p.m. Pet'rs' Ex. 3 at 3; Pet'rs' Ex. 4 at 3. He was moved to his crib, which he shared with his twin, at approximately 11:30 p.m. *Id.*

Ms. Nunez wrote that J.J. usually “slept through the night from 11 p.m. until 8 a.m.” Pet’rs’ Ex. 3 at 3. Ms. Nunez described checking on J.J. and his twin sister the next morning at 8:00 a.m., when she found them both sleeping. *Id.*; Pet’rs’ Ex. 39 at 3. Mr. Diaz wrote that at around 9:15 a.m., he “heard that [J.J.’s twin] was up and immediately went in to get her so she would not wake [J.J.] if he was still asleep.” Pet’rs’ Ex. 4 at 3. Mr. Diaz wrote that J.J. was still asleep at that time, so he took J.J.’s twin out of the room to change and feed her. *Id.* Mr. Diaz also wrote that when Ms. Nunez arrived home, she “immediately went in to check on [J.J.] since he never slept that late.” *Id.* Ms. Nunez wrote that when she found J.J., his “eyes were open and his mouth was blue” but he was warm. Pet’rs’ Ex. 3 at 4; *see also* Pet’rs’ Ex. 39 at 3. Mr. Diaz described J.J. in the same manner. Pet’rs’ Ex. 4 at 3. Ms. Nunez wrote that she began CPR, which caused the “blueness around his mouth [to go] away,” but “a lot of mucus [was] coming out of his mouth and nose.” Pet’rs’ Ex. 3 at 4; *see also* Pet’rs’ Ex. 4 at 3. The parents wrote that an ambulance arrived around 15 minutes later, and J.J. was taken to the hospital where they were told he had died. *Id.*; Pet’rs’ Ex. 39 at 3.

### C. Fact Testimony

Ms. Nunez did not initially describe J.J.’s health on the day of his four-month well-baby visit during her testimony. On cross-examination and re-direct, both counsel referenced her written statements describing J.J.’s “runny nose” and “productive cough” at the time of that visit. Tr. 20:14–15, 22:5–10. Ms. Nunez affirmed those statements. Tr. 20:16, 22:11. Ms. Nunez then testified that J.J. had a stuffy nose in October of 2012 that was “no longer stuffy on the day of his appointment . . .” Tr. 22:14–22. She testified that his stuffy nose occurred in the beginning of October, and she administered saline drops “for a couple of days” until J.J. “had just a runny nose, [which] was from [her] giving him saline drops.” Tr. 23:14–23. She emphasized that the stuffy nose from early October went away and was replaced by the runny nose, which “got better” with time. Tr. 23:24–24:4. Ms. Nunez clarified that “he still had [the runny nose], but just not so often.” Tr. at 24:6–7. She testified that on the day of his four-month appointment, his nose was “just runny” with “very light, clear . . . mucus,” which she attributed to allergies. Tr. 22:18–21. She stated that “he had a cough as well” during the appointment, but she said it was “less” of a cough than when it started with the congestion in early October. Tr. 22:21–22, 24:10–16. Ms. Nunez denied that she was “concerned about the stuffy nose, the runny nose[,] or the cough” on the day of J.J.’s four-month visit. Tr. 24:19–21.

Ms. Nunez stated that, other than being “a bit cranky” and “[a] bit more fussy,” J.J. was behaving normally and “it was just like another day” after his four-month appointment. Tr. at 14:16–22. She stated that J.J. was fed approximately twice before being put to bed. Tr. 14:23–15:2. Ms. Nunez testified that J.J. was both breast- and bottle-fed. Tr. 21:20–23.

Ms. Nunez testified that J.J. and his twin sister slept together in one crib, lying with space between them and their heads on opposite ends of the crib. Tr. 13:4–9. The crib contained a crib sheet and a thin receiving blanket tucked “under [J.J.’s] waist [and] around his thighs and leg area.” Tr. 15:3–12. There were no bumpers, blankets, bedding, stuffed animals, or pillows in the crib. Tr. 15:10–11. Ms. Nunez testified that she never placed J.J. on his belly when putting him to sleep, and J.J. was not yet able to roll over on his own. Tr. 15:23–16:8.

Ms. Nunez testified that she woke up at around 6:30 a.m. the next day to get J.J.'s older sister ready for school. Tr. 17:1–3. She saw J.J. “sleeping on his back [in] the same position [she] left him [i]n, [with] the blanket still . . . around his thighs [and] under his waist,” at approximately 6:45 a.m. Tr. 17:5–8.

Ms. Nunez's testimony with respect to the chronology immediately following J.J.'s vaccination and leading up to his death was consistent with the information provided in the affidavits filed in this case. Ms. Nunez's responses to questions regarding the severity of J.J.'s symptoms on the date of his vaccination and his mobility were less clear. For example, Ms. Nunez's testimony regarding whether J.J. could successfully roll over or push up when he “would try to roll his neck and just like push his hands . . . .” was inconsistent. Tr. 21:7–12. Also, Ms. Nunez testified that she pointed out J.J.'s symptoms of cough and runny nose to the doctor on the day of J.J.'s vaccinations, but she testified that she was not concerned about either at the time. Tr. 24:19–21.

### **III. Expert Review**

#### **A. Expert Qualifications**

##### **1. Petitioners' Expert, Douglas C. Miller, M.D., Ph.D.**

Petitioners' expert, Dr. Douglas Miller, authored three expert reports and testified at the entitlement hearing. Pet'rs' Exs. 12, 37, 38, ECF Nos. 21-2, 44-1, 71-1; Tr. 26–122, 338–371. Dr. Miller is a neuropathologist with experience in academia and forensic practice. Pet'rs' Ex. 12 at 1. He is board certified in anatomic pathology and neuropathology. *Id.* He currently serves as a clinical professor in the Department of Pathology and Anatomical Sciences at the University of Missouri School of Medicine, where he has been employed since December 2007. *Id.*

Dr. Miller has published more than 150 articles and book chapters, co-authored a text-atlas of neurology, and is the sole author of a surgical neuropathy text. *Id.* at 2. In addition to academia, he has been a consultant neuropathologist for various hospitals and medical examiners. *Id.* He currently serves as associate medical examiner as part of his duties at the University of Missouri, where his office provides forensic autopsy services throughout the state. *Id.* His neuropathology experience includes analysis of infant deaths where SIDS is suspected. *Id.* Dr. Miller testified that in his current position, he completes “the neuropathology parts of autopsies” with residents. Tr. 29:3–4. Dr. Miller has “been an expert witness in many legal cases, both civil and criminal, including many infant deaths in which SIDS has been either suspected prior to autopsy or suggested as an alternative diagnosis to one of traumatic brain injury.” Pet'rs' Ex. 12 at 2. Dr. Miller has testified three times in the United States Court of Federal Claims regarding potentially vaccine-related injuries and deaths. *Id.*

Dr. Miller is not an immunologist. Tr. 87:10–12. Dr. Miller does not have educational or clinical experience in pediatrics. Tr. 87:13–14. At the hearing, Petitioners did not seek to admit Dr. Miller as an expert in any specific area. Respondent, however, did not object to Dr. Miller's testimony, and the undersigned did not limit his testimony. Based off Dr. Miller's filed CV and his testimony describing his research and practice areas, the record provides evidence that his

expertise lies in neuropathology. Dr. Miller has also testified previously in the Program as an expert in neuropathology, specifically in cases that alleged vaccine-caused SIDS. *Jewell*, 2017 WL 7259139; *Boatmon v. Sec’y of Health and Human Servs.*, No. 13-611V, 2017 WL 3432329 (Fed. Cl. Spec. Mstr. Jul. 10, 2017); *Copenhaver v. Sec’y of Health & Human Servs.*, No. 13-1002V, 2016 WL 3456436 (Fed. Cl. Spec. Mstr. May 31, 2016); *Lord v. Sec’y of Health & Human Servs.*, No. 12-255V, 2016 WL 806818 (Fed. Cl. Spec. Mstr. Feb. 9, 2016).

## **2. Respondent’s Expert Rebecca D. Folkerth, M.D.**

Dr. Rebecca Folkerth issued two reports in this case and testified at the entitlement hearing on behalf of Respondent. Resp’t’s Exs. C, F, ECF Nos. 41-1, 56-1; Tr. 122–177. Dr. Folkerth received her medical degree from the University of Louisville School of Medicine. Resp’t’s Ex. C at 2. She completed her residency in anatomic pathology and a fellowship in neuropathology before establishing a practice at Brigham and Women’s Hospital Department of Pathology. *Id.* Dr. Folkerth holds board certifications in anatomic pathology, neuropathology, and cytopathology. *Id.* Dr. Folkerth is a clinical associate professor at New York University School of Medicine in the Forensic Medicine Department and the neuropathologist for the Office of the Chief Medical Examiner in New York City. Tr. 124:7–10. She has written over 100 peer-reviewed articles covering various issues in pathology. Resp’t’s Ex. C at 2.

The undersigned finds that Dr. Folkerth’s testimony was generally consistent with the filings and essentially limited to a discussion of whether J.J.’s death was properly categorized as SIDS. There was no disagreement between the parties that J.J.’s death was properly categorized as SIDS, and on cross-examination, Dr. Folkerth was asked whether J.J. had a brainstem defect that made him more vulnerable to SIDS. Dr. Folkerth stated that given his brainstem gliosis, “[i]t’s probably likely, more likely than not” that J.J. had a defective medullary serotonergic system. Tr. 134:3–6. She does not, however, believe that this is “necessarily indicative of a vulnerability to SIDS.” Tr. 133:13–14. Instead, Dr. Folkerth opined that the gliosis “is a marker for whatever leads to various apneic periods” and should be seen as “an indicator of some sort of previous mild or chronic hypoxic ischemic changes.” Tr. 133:24–25.

## **3. Respondent’s Expert Dr. Christine McCusker, M.D.**

Dr. Christine McCusker authored two expert reports and testified during the hearing on behalf of Respondent. Resp’t’s Exs. A, E, ECF Nos. 37-1, 51-1; Tr. 178–337. She received her Master of Science in Molecular Virology and Immunology and her M.D. from McMaster University in Hamilton, Ontario. Resp’t’s Ex. B at 1, ECF No. 37-2; Tr. 178:25–179:1. Dr. McCusker then completed a clinical fellowship in allergy and immunology at McGill University in Montreal, Quebec. *Id.* at 2. She is board certified in pediatrics and currently works as a staff physician in the Emergency Department and an associate professor in the Department of Pediatrics, Division of Allergy and Immunology (Pediatric) of Montreal Children’s Hospital and McGill University. *Id.* at 2–3.

Dr. McCusker has taught several courses at the undergraduate and graduate levels on biochemistry, cytokines, and the development of the immune system in infancy. Tr. 181:20–182:3. She has published peer-reviewed articles on pediatric immunology and specifically cytokine

activation. *See* Resp't's Ex. B. Dr. McCusker has testified previously in the Program, specifically in cases that allege vaccine-caused SIDS. *Jewell*, 2017 WL 7259139; *Boatmon*, 2017 WL 3432329.

## **B. Sudden Infant Death Syndrome and the Triple Risk Model**

Dr. Miller opined that “there is no evidence of any acute process in the brain which would have been a cause of death” for J.J., such as meningitis. Pet'rs' Ex. 12 at 4; *see* Tr. 33:22–24. Dr. Miller stated that J.J.'s death was properly categorized as a SIDS death. Tr. 39:21–22. He emphasized that “SIDS is a syndrome, not a disease[.]” Pet'rs' Ex. 38 at 4. He testified that SIDS “has lots of different potential causes, not all of which are fully understood.” Tr. 39:18–20. Dr. Folkerth similarly noted that the medical examiner “designated the cause of death as ‘Sudden Unexpected Death in Infancy.’” Resp't's Ex. C at 5. Dr. Folkerth further opined “that this case falls into the category of SUDI/SIDS.”<sup>10</sup> *Id.* at 6. Dr. McCusker also noted that the coroner ruled that SIDS was the cause of death. Resp't's Ex. A at 2.

Dr. Miller opined that J.J. meets the criteria for the “Triple Risk Model” of SIDS, which was “formulated by Dr. Hannah Kinney quite a few years ago.” Pet'rs' Ex. 12 at 4 (citing Pet'rs' Ex. 14, ECF No. 91-2<sup>11</sup>). Dr. Folkerth agreed that “[t]he prevailing concept of SUDI/SIDS is that proposed by Kinney and colleagues, [i.e.,] the ‘Triple Risk Model[.]’” Resp't's Ex. C at 5. Dr. McCusker also discussed the Triple Risk Model in her reports and considered J.J.'s case under that model. *See* Resp't's Ex. A at 2–3; Resp't's Ex. E at 2–6.

The Triple Risk Model, as described by Dr. Kinney and Dr. Filiano in a 1994 article, proposes that “sudden death in SIDS results from the intersection of three overlapping factors: (1) a vulnerable infant; (2) a critical developmental period in homeostatic control[;] and (3) an exogenous stressor[ or stressors].” Pet'rs' Ex. 14 at 1–2.<sup>12</sup> Under the model, “an infant will die of SIDS only if he/she possesses all three factors; the infant's vulnerability lies latent until he/she enters a critical developmental period and is subject to an exogenous stressor which matches the infant's underlying vulnerability and overwhelms an already compromised homeostatic system.” *Id.* at 2. Furthermore, “death occurs only if all three factors intersect and only if the exogenous stressor matches the specific vulnerability of the individual infant[.]” *Id.* at 3. Therefore, “the infant may survive as ‘normal,’” despite an underlying vulnerability, “if the stressor is avoided, or if the underlying vulnerability is ameliorated by therapeutic interventions.” *Id.*

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<sup>10</sup> Dr. Folkerth testified that “SUDI is a more generalized term” than SIDS. Tr. 129:23. She explained that a death is classified as a “sudden unexpected death in infancy,” or SUDI, “any time an infant dies suddenly and unexpectedly.” Tr. 129:9–12. She continued that the autopsy and related investigations may reveal the cause for a subset of SUDI cases such that “they[ are] no longer an unexplained death.” Tr. 129:12–17. However, if the death remains unexplained, then it is classified as a SIDS death. Tr. 129:17–22.

<sup>11</sup> James J. Filiano & Hannah C. Kinney, A Perspective on Neuropathologic Findings in Victims of the Sudden Infant Death Syndrome: The Triple-Risk Model, 65 BIOL. NEONATE 194 (1994).

<sup>12</sup> When medical literature is referenced in this opinion, the undersigned will cite to the CM/ECF page numbers of the filed documents rather than the page numbers of the articles as they appeared in the journals or other original sources.

Dr. Kinney’s model favors “evidence [that] suggests that SIDS involves a convergence of stressors that probably results in the asphyxia of a vulnerable infant who has . . . defective . . . defense systems . . .” Pet’rs’ Ex. 37, Tab C at 8, ECF No. 93-4.<sup>13</sup> The research has not identified “a universally accepted biologic explanation” for SIDS; however, the “current understanding . . . reflects the simultaneous juxtaposition of multiple events that, when taken individually, are far less powerful than the result of their chance combination.” *Id.*

## **1. Vulnerability under the Triple Risk Model**

### **i. “Intrinsic Risk Factors” of Male Gender and Prematurity**

Vulnerability is not clearly defined by any of the experts or the medical literature, but the designation serves to identify the pool of infants that are more likely to suffer from SIDS using their common traits. These traits, or intrinsic risks, are genetic or environmental in nature and affect susceptibility, such as prenatal exposure to cigarettes and maturity at birth. Resp’t’s Ex. A, Tab 5 at 2, ECF No. 38-5.<sup>14</sup> The 1994 article by Dr. Kinney and Dr. Filiano considers such “epidemiologic risk factors” in the discussion of “[t]he concept of the vulnerable infant.” Pet’rs’ Ex. 14 at 2. These types of factors “point to a suboptimal intrauterine environment[] and suggest that the mechanisms for risk for SIDS develop in fetal life in at least some cases.” *Id.* Male infants are also identified as potentially more vulnerable to SIDS. There is “mounting evidence” in studies done with mice that “sexually dimorphic features in the brain[]” manifest as “differences in brainstem-mediated 5-[hydroxytryptamine (“5-HT”)] function, with females’ brains apparently relying less on 5-HT neurons in chemoreception and adapting more readily to the loss of 5-HT function.” Pet’rs’ Ex. 20 at 11, ECF No. 91-8.<sup>15</sup> These studies help to identify potential markers for vulnerability, such as gender, and shed light on the biological systems that are affected in SIDS cases, such as the brainstem. *Id.* Intrinsic risk factors also include identification markers that indicate a statistically increased risk of SIDS, but the specific effect of the marker remains unclear, such as the sub-Saharan African descent marker denoting race.<sup>16</sup> *Id.* at 4.

Intrinsic risk factors were discussed by each expert in varying contexts. At times, intrinsic factors were discussed in relation to infant vulnerability, and at other times they were considered in combination with certain other “risk factors” that fall into the category of exogenous stressors. *See, e.g.*, Tr. 81; Pet’rs’ Ex. 37 at 6; Resp’t’s Ex. C at 5. Dr. McCusker also discussed intrinsic risk factors as part of her “critical window” analysis. Resp’t’s Ex. E at 3–4. All the experts agreed that J.J. was born prematurely and was a male, and that both of those facts increased his relative risk of SIDS. Tr. 51: 16–23, 81:4–6, 134:24, 172:10–12, 208:13–14; Resp’t’s Ex. C at 5; Resp’t’s Ex. E at 3–4. They do not all agree, however, on whether J.J. qualified as a “vulnerable infant” under the Triple Risk Model. J.J.’s male gender and prematurity certainly did not *cause* him to

<sup>13</sup> Hannah C. Kinney & Bradley T. Thach, *The Sudden Infant Death Syndrome*, 361 N. ENGL. J. MED. 795 (2009).

<sup>14</sup> Felicia L. Trachtenberg et al., *Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign*, 129 PEDIATRICS 630 (2012).

<sup>15</sup> Hannah C. Kinney et al., *The Brainstem and Serotonin in the Sudden Infant Death Syndrome*, 4 ANN. REV. PATHOL. 517 (2009).

<sup>16</sup> The article designates “African-American” as a race, however, African-American is not a race. Pet’rs’ Ex. 20 at 4.

die from SIDS, but both are specifically identified by Dr. Kinney as risk factors that would have statistically increased his chances of suffering from SIDS.

## ii. Brainstem Defects

Dr. Miller testified that one major potential vulnerability under the Triple Risk Model is a developmentally defective medulla. He explained that medical and scientific literature has shown that “the brain structures responsible for regulation of respiration, including those that sense increased blood carbon dioxide levels during sleep and respond[] to them with arousal and increased (gasping) breathing, reside in the medulla in a network of nuclear structures which use serotonin as their neurotransmitter.” Pet’rs’ Ex. 12 at 4 (citing Pet’rs’ Exs. 15–21, ECF Nos. 91–3–9<sup>17</sup>). He further explained that “there are several sets of neurons in the medulla in different locations which have related but different functions” associated with “sensing how much carbon dioxide there is in the blood” and stimulating respiratory drive and arousal from sleep. Tr. 43:11–18. This “system of nerve cells . . . use[s] the transmitter serotonin” 5-HT.<sup>18</sup> Tr. 43:9–11. He also wrote that “[t]he arcuate nuclei are one important member of this network[.]” Pet’rs’ Ex. 12 at 4. In his testimony, Dr. Miller stated that based on what is known from animal data, the arcuate nucleus is “the primary carbon dioxide sensor in the brain.” Tr. 43:23–25. Therefore, he opined that “[a] critical structure to examine in the brain of a potential SIDS case is the arcuate nucleus in the ventral medulla.” Pet’rs’ Ex. 12 at 4 (citing Pet’rs’ Ex. 13, ECF No. 91–1<sup>19</sup>). Dr. Miller noted that infants with defects in the brain structures responsible for respiratory regulation are thought to make up as much as 70 percent of the SIDS population. Pet’rs’ Ex. 12 at 4; *see also* Pet’rs’ Ex. 20 at 6.

Dr. Miller explained that “[i]n an infant with such a defective brainstem, during the period of early post-natal life before full maturation of brain systems that regulate heart rate, respiratory activity, sleep, and related autonomic functions, one or more external ‘stressors’” can cause a life-

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<sup>17</sup> Pet’rs’ Ex. 15, Hannah C. Kinney et al., *Medullary Serotonergic Network Deficiency in the Sudden Infant Death Syndrome: Review of a 15-Year Study of a Single Dataset*, 60 J. NEUROPATHOLOGY & EXPERIMENTAL NEUROLOGY 228 (2001); Pet’rs’ Ex. 16, Hannah C. Kinney et al., *Subtle Developmental Abnormalities in the Inferior Olive: An Indicator of Prenatal Brainstem Injury in the Sudden Infant Death Syndrome*, 61 J. NEUROPATHOLOGY & EXPERIMENTAL NEUROLOGY 427 (2002); Pet’rs’ Ex. 17, Hannah C. Kinney, *Brainstem Mechanisms Underlying the Sudden Infant Death Syndrome: Evidence from Human Pathologic Studies*, 51 DEVELOPMENTAL PSYCHOBIOLOGY 223 (2009); Pet’rs’ Ex. 18, Hannah C. Kinney et al., *The Serotonergic Anatomy of the Developing Human Medulla Oblongata: Implications for Pediatric Disorders of Homeostasis*, 41 J. CHEMICAL NEUROANATOMY 182 (2011); Pet’rs’ Ex. 19, Kevin J. Cummings et al., *Postnatal Loss of Brainstem Serotonin Neurones Compromises the Ability of Neonatal Rats to Survive Episodic Severe Hypoxia*, 589 J. PHYSIOLOGY 5247 (2011); Pet’rs’ Ex. 20, Kinney et al., *supra* note 15; Pet’rs’ Ex. 21, David S. Paterson et al., *Medullary Serotonin Defects and Respiratory Dysfunction in Sudden Infant Death Syndrome*, 168 RESPIRATORY PHYSIOLOGY NEUROBIOLOGY 133 (2009).

<sup>18</sup> Dr. Miller explained in his testimony that serotonin is a synaptic neurotransmitter, “a chemical molecule that neurons use to communicate from one cell to the next across a gap, which is called a synapse.” Tr. 47:9–11. Specifically, serotonin is “an excitatory synaptic transmitter,” which “is supposed to increase activity” in the target neuron. Tr. 47:12–16.

<sup>19</sup> James J. Filiano & Hannah C. Kinney, *Arcuate Nucleus Hypoplasia in the Sudden Infant Death Syndrome*, 51 J. NEUROPATHOLOGY & EXPERIMENTAL NEUROLOGY 394 (1992).

threatening situation in one of two ways. Pet'rs' Ex. 38 at 4. External stressors can “suppress the normal homeostatic responses mediated by this medullary serotonergic network, leading to a failure of homeostasis and death.” *Id.* Alternatively, external stressors “can create a dangerous situation, such as apnea, to which the medullary mechanisms which ought to respond by producing arousal just fail to do so.” *Id.*

Dr. Miller explained that all humans “experience periods of apnea” during sleep, meaning that there are periods where “we stop breathing in sleep.” Tr. 45:22–23. Normally, the period is brief and a person wakes up, “or at least arouse[s] enough to breathe again.” Tr. 45:23–25. If pillows or other objects are obstructing an infant’s face, the infant will re-inhale carbon dioxide-rich air, which will lead to an increase in blood carbon dioxide levels. Tr. 46:9–19. Under normal circumstances, if the body’s “level of CO<sub>2</sub> rises above a safe level during sleep, the arcuate nuclei should detect that[] and respond by signaling through their neurotransmitter serotonin to other nuclei in the network to stimulate arousal and gasping respirations.” Pet'rs' Ex. 38 at 4–5. Dr. Miller wrote that it is “suppression of this network’s activity” that is thought to provoke SIDS in a vulnerable infant. *Id.* at 5. Infants with “various different defects in the medulla,” particularly where the “arousal mechanism, which is mediated by serotonin neurons, is defective,” will not wake up. Tr. 46:25–47:3. As a result, carbon dioxide levels continue to rise, eventually leading to death. Tr. 47:3–6. Dr. Miller explained that under the Triple Risk Model, “there are various things which can cause stress on the brainstem functions, which then get no response or an inadequate response” from the defective arousal mechanism when there is an apnea event. Tr. 46:1–7.

Dr. McCusker also acknowledged that studies suggest that infants who die of SIDS may have “intrinsic defects in the autonomic nervous system with inadequate compensation[,] which when stressed[,] can lead to death.” Resp’t’s Ex. E at 3 (citing Resp’t’s Ex. E, Tab 1, ECF No. 52-1;<sup>20</sup> Tab 4, ECF No. 52-4<sup>21</sup>). Dr. Folkerth did not explicitly discuss in her reports whether brainstem defects or abnormalities can make an infant “vulnerable” under the Triple Risk Theory. Instead, Dr. Folkerth wrote that “the finding by Dr. Kinney and others that a subset of infants dying of SIDS . . . has brainstem abnormalities detected using research tools means only that there is a biologically plausible basis for an intrinsic abnormality of the brainstem that leaves an infant at risk for death when confronted by potential stressors[.]” Resp’t’s Ex. F at 2. She emphasized that “a brainstem abnormality (such as arcuate nucleus hypoplasia)” is not required for a diagnosis of SIDS. *Id.*

#### **a. The Autopsy Procedure**

Dr. Miller criticized the examination of the brain in this case, describing it as “suboptimal.” Pet'rs' Ex. 12 at 3. Dr. Miller explained that “[t]here is only one level of medulla available for histological examination[.]” *Id.* Furthermore, he explained that “[t]he hippocampus section is overly small, and at a rather more anterior level than is ideal for examination.”<sup>22</sup> *Id.* at 3–4.

<sup>20</sup> Kinney & Thach, *supra* note 13.

<sup>21</sup> André Kahn et al., *Sudden Infant Deaths: Stress, Arousal and SIDS*, 75 EARLY HUM. DEV. S147 (2003).

<sup>22</sup> Dr. Miller argued that sectioning all levels of the medulla would be “best practice[.]” to rule out the absence of the arcuate nucleus or hypoplasia in a SIDS autopsy. Pet'rs' Ex. 37 at 2. In support of that argument, he noted that experts retained by the Department of Health and Human Services have previously

Additionally, Dr. Miller wrote that the review of the hippocampus slide “is further limited by a poor histological preparation, with the tissue in fragments, not in one piece.” *Id.* at 4. Finally, Dr. Miller explained that “[t]here is only one other sample with any cerebral cortex, [and that sample is] also small and inadequate.” *Id.* Dr. Miller noted that there is “more gliosis than Dr. Mena described, including in the frontal cortex, in the frontal white matter, and in the cerebellar white matter.” *Id.* Dr. Miller testified that “the gliosis didn’t happen the day [J.J.] died” and that it could be evidence of prior episodes of adverse events. Tr. 92:24–25. He noted that “[g]liosis is a process which takes days to evolve,” and that it can exist in a brain for “weeks or years.”<sup>23</sup> Tr. 92:25–93:5.

Dr. Folkerth did not agree with Dr. Miller’s assessment that the brain examination was “suboptimal,” because she explained that “only one level of the medulla is necessary to confirm an impression of SUDI/SIDS.” Resp’t’s Ex. C at 6. She wrote that studies which have “detected abnormalities in the medulla, principally of the serotonergic system,” rely on “*research* methods (i.e., specialized biochemical, cell-counting, and other techniques)[ ] not available to forensic or hospital pathology practitioners for *diagnostic* purposes.” *Id.* (emphasis in original). She also wrote that “the lack of complete sectioning of the entire medulla in no way decreases the likelihood that the child died of SUDI/SIDS[,]” and that “an examination of the entire medulla[ ]” is not required to find a diagnosis of SIDS. *Id.* Dr. Folkerth opined that the brain sections available for review were “adequate for the purposes of detecting alternate causes of death (such as encephalitis, malformations, etc.).” *Id.* She concluded that “the sampling of the brain was within [the] standard of care[.]” Resp’t’s Ex. F at 2.

#### **b. J.J.’s Brain**

Dr. Miller testified that the autopsy of the brain in this case showed “markers” of defects associated with the medulla. Tr. 48:2–4. Dr. Miller opined that “the [arcuate] nuclei in the single section available” from the examination performed in this case “are at least somewhat hypoplastic,”<sup>24</sup> but this may just be due to the level of the section, as the nucleus varies in size from level to level.” Pet’rs’ Ex. 12 at 4. He emphasized in his testimony that the single slide of medulla available “has arcuate nuclei that in [his] judgment are too small,” and that the single slide is “the only evidence [he] ha[s] to go on.” Tr. 115:22–24; *see also* Tr. 81: 9–14. He also noted that the nucleus is “mildly gliotic,” which, he stated, “goes along with the gliosis Dr. Mena did record in the adjacent inferior olivary nuclei.” Pet’rs’ Ex. 12 at 4. Based on his overall review of the autopsy slides, Dr. Miller opined that “there is definite evidence of brainstem impairment in this infant,

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opined that “the absence of any arcuate nuclei in a single section of medulla is insufficient evidence for a brainstem defect[.]” *Id.* at 4. Dr. Miller opined that “[w]hen there are negative findings[,]” such as a finding that there were no abnormalities, “one must ask about the adequacy of the examination[.]” *Id.* In Dr. Miller’s opinion, the sampling Dr. Mena provided is not adequate. *Id.*

<sup>23</sup> He noted that “there was gliosis, which is a sign of ongoing cellular damage[,] in several of the areas” where serotonergic neurons exist, including the arcuate nuclei and the inferior olivary nuclei. Tr. 48:9–12. He testified that additional areas of generalized gliosis were found in the brain, “including in the cerebral hemispheres,” which, he testified, “indicat[es] that there had probably been prior episodes of perhaps lower oxygen or higher carbon dioxide,” possibly related to J.J.’s prematurity. Tr. 48:19–24.

<sup>24</sup> Hypoplasia is the “incomplete development or underdevelopment of an organ or tissue.” *Dorland’s* at 905.

especially of the medulla.” *Id.* Dr. Miller emphasized that “there is evidence in the autopsy that [J.J.] had some of the brainstem defects reported as indicative of vulnerability to SIDS . . . and he presumptively had a defective medullary serotonergic system as the cause of his vulnerability.” Pet’rs’ Ex. 37 at 6. Therefore, Dr. Miller opined that J.J.’s “maldeveloped or damaged medulla” qualifies him as a “vulnerable infant” under the Triple Risk Model. Pet’rs’ Ex. 12 at 4. His opinion was based in part on “the evidence of gliosis in the brain stem, and particularly in the medulla.” Tr. 93:14–15. It was also based on his opinion that “in the slide that’s available of the medulla, the arcuate nucleus is hypoplastic.” Tr. 94:10–12. Additionally, Dr. Miller testified that he made a “statistical inference” based on the fact that 70 percent or more of infants who die from SIDS “have defects in the serotonergic system in the medulla” at autopsy. Tr. 93:17–20.

Dr. Folkerth wrote in her report that “[a] single section of the medulla may or may not show . . . aplasia or hypoplasia of the arcuate nucleus[.]” Resp’t’s Ex. C at 6. She did not provide an opinion in her reports as to whether J.J. may have had a brain defect that would qualify him as a vulnerable infant. She wrote only that “[t]he arcuate nucleus was present in the medulla.” *Id.* at 5. In her testimony, Dr. Folkerth opined that a single section of medulla is “adequate to exclude a diagnosis of hypoplasia for the most part.” Tr. 131:22–25. She testified that she could not remember and did not write anything down about the arcuate nuclei “appearing small or otherwise abnormal” upon her review of the slide. Tr. 131:25–132:2. Therefore, she testified that she did not “feel that there were enough grounds to say anything regarding arcuate hypoplasia,” and later opined more definitively that she does not “think the arcuate nucleus is small.” Tr. 132:2–4, 137:10–11. Dr. Folkerth wrote in her report that the “[d]eep cerebral white matter had some prominent reactive astrocytes.” Resp’t’s Ex. C at 5. Additionally, Dr. Folkerth noted that “[s]ections of midbrain, pons, and medulla were notable for rare reactive astrocytes in the median raphe[] and in the inferior olivary nucleus.” *Id.* Dr. Folkerth opined that “[g]liosis is a result of any kind of injury,” and is therefore “not specific in the least.” Tr. 130:24–25. She agreed with Dr. Miller’s assessment that “they’re sort of the scar cells of the brain,” noting that they can be seen “following all sorts of processes,” such as “infection[, lack of] oxygen[, or] actual mechanical trauma or seizures.” Tr. 131:2–10. Dr. Folkerth opined that gliosis does not “necessarily have a lot of significance when [it is] very limited, as in this case.” Tr. 131:15–16. Dr. Folkerth further opined that evidence of gliosis is “not necessarily indicative of a vulnerability to SIDS.” Tr. 133:13–14. She testified that gliosis is “a marker for whatever leads to various apneic periods that result in gliosis.” Tr. 133:23–24.

Despite her opinions regarding the autopsy findings, Dr. Folkerth conceded that J.J. “could very well have had, [and] probably did have[, ] an intrinsic brain stem abnormality.” Tr. 159:1–3. Dr. Folkerth testified that J.J.’s “brain stem was not studied to look for specific serotonergic defects, so none of us in this room can say whether he had them or not.” Tr. 137:23–138:1. Continuing, she testified that “based on the information we have [and] using the routine diagnostic standards that we use, [she] think[s] [J.J.’s death] completely fits a SIDS picture.” Tr. 138:1–3. Thus, she explained that “we’re sort of inferring that since J.J. died of SIDS and since most babies who die of SIDS have a brain stem defect, more likely than not he did.” Tr. 168:25–169:2.

Dr. Folkerth wrote that a “vulnerable infant” under the model has “features such as premature delivery, exposure to cigarette smoke, [or] male gender[, ]” and she noted that both prematurity and male gender are applicable in this case. Resp’t’s Ex. C at 5–7.

Based on all the evidence, the undersigned finds that it is more likely than not that J.J. had a brain defect which, along with his male gender and prematurity, qualified him as a “vulnerable infant” under the Triple Risk Model of SIDS. Dr. Miller persuasively opined that the arcuate nuclei in the single section of medulla available for examination were “at least somewhat hypoplastic[.]” Pet’rs’ Ex. 12 at 4. Dr. Folkerth agreed that, statistically, “[i]t’s probably likely, more likely than not,” that J.J. had a defective medullary serotonergic system.<sup>25</sup> Tr. 134:4–6. Ideally, multiple slides of the medulla would be available to the parties’ experts so that they could determine definitively whether the arcuate nuclei were hypoplastic. However, as Dr. Folkerth stated, the methods used to “detect[] abnormalities in the medulla, principally of the serotonergic system,” are research methods which are “not available to forensic or hospital pathology practitioners[.]” Resp’t’s Ex. C at 6. In Program cases involving infant deaths, petitioners must rely on results from the procedures used by those practitioners,<sup>26</sup> and it would be unfair to expect hospital pathologists, while determining a cause of death, to replicate the type of comprehensive examination done in research settings to study etiology. The Program does not ever require medical certainty, and in this case, there is supporting evidence and the experts agree that statistically speaking a condition is more likely than not present. It is enough for Petitioners to establish it is more likely than not that J.J. had a defective brainstem and was a vulnerable infant as defined by Dr. Kinney’s Triple Risk Model.

## **2. The Critical Development Period under the Triple Risk Model**

The critical development period is defined by Dr. Kinney as the first year of life, with “the peak age being between 2–4 months of age.” Resp’t’s Ex. E at 3. The window of time is significant because it “coincides with progression both in brain and in lung development.” *Id.* at 3–4. All three experts reviewed the medical records and concur that J.J. died from SIDS the day after his receipt of four vaccines that were administered during his four-month well-baby examination. This fits squarely within the critical development period and is not in dispute.

## **3. Exogenous Stressors under the Triple Risk Model**

An exogenous stressor, or “extrinsic risk,” is “defined as a physical stressor around the time of death that may increase the risk of SIDS for an already vulnerable infant.” Resp’t’s Ex. A, Tab 5 at 2–3. Dr. McCusker cited Dr. Kinney’s findings from a 2012 study that found that ninety-nine percent of SIDS infants “had at least 1 [intrinsic or extrinsic] risk factor.” Resp’t’s Ex. A at 3 (citing Resp’t’s Ex. A, Tab 5 at 3). Dr. Kinney reported in that same study that “75% [of SIDS infants] had at least 1 of each [extrinsic and intrinsic risk factor]” and “[t]he majority

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<sup>25</sup> Dr. Folkerth noted that she could not be certain without conducting a study such as the one Dr. Kinney uses in her research. Tr. 134:7–11. Dr. Folkerth emphasized that “about 70 percent of SIDS infants do turn out to have these abnormalities after [researchers] do research on them, but . . . that is not determined by the routine standard neuropathologic examination that[ is] available . . . in medical examiners’ offices.” Tr. 134:12–18.

<sup>26</sup> Dr. Folkerth testified that “the guidelines are sort of loose among all medical examiners’ offices about exactly what should be submitted.” Tr. 132:11–14. Dr. Folkerth added that if she can include two sections of the medulla, she will do so in order to “feel more sure that [she is] seeing . . . representational tissue.” Tr. 132:14–17.

(57%) had at least 2 extrinsic risks and 1 intrinsic risk factor.” Resp’t’s Ex. A, Tab 5 at 3. Dr. McCusker testified that “there is a suggestion that there is an increased frequency of sudden infant death if there is more than one risk factor,” although the total number of risk factors “doesn’t appear to . . . make a difference.” Tr. 268:23–269:5. She also noted that “you can have sudden infant death with none” of the identified risk factors present. Tr. 269:9.

Dr. McCusker explained that “extrinsic factors,” which have been “identified through the epidemiological studies,” are “those elements which may contribute to a change in the mechanics of respiration, as opposed to the neurochemical.” Resp’t’s Ex. A at 3. She also described them as “those factors that are consistent with hypoxia[-]generating conditions[.]” Resp’t’s Ex. E at 5, (citing Pet’rs’ Ex. 37, Tab C<sup>27</sup>). She listed “prone or side sleeping, bed sharing, over-bundling, soft bedding, [having one’s] face covered[,], upper respiratory tract infection[,], . . . parental, especially maternal smoking[,], . . . bottle feeding[,], smoking in the home[,],” and “GE reflux” as examples of external risk factors. Resp’t’s Ex. A at at 3, 9. She noted that “[h]igher ambient temperatures” created by bundling or use of covers “are also considered risk factors for SIDS [because they] inhibit[] respiratory drive and reduc[e] the normal heart-rate variability without raising core body temperature.” Resp’t’s Ex. E at at 5 (citing Resp’t’s Ex. A, Tabs 1,<sup>28</sup> 4,<sup>29</sup> 15,<sup>30</sup> ECF Nos.38-1, 38-4,39-5).

Dr. McCusker wrote that, “[i]n the case of [J.J.], he was **co-sleeping**, was known to be a **bottle[-]fed** baby[,], and had symptoms of an **upper respiratory tract infection**.” Resp’t’s Ex. A at 3 (emphasis in original); *see also* Resp’t’s Ex. E at 5 (Dr. McCusker’s second report, describing bed sharing, bottle feeding, and “upper respiratory tract infection (per his parents)” as risk factors). As discussed previously, Dr. McCusker also identified prematurity and male gender as risk factors in J.J. Resp’t’s Ex. A at 9. Dr. Folkerth noted that J.J. “was born prematurely[] and had additional known risk factors of a potentially unsafe sleeping environment (co-sleeping with his twin), and male gender.” Resp’t’s Ex. C at 7. She also noted that Petitioners’ affidavits identified that J.J. had a runny nose and cold, which she testified “probably represented a risk factor.” Tr. 135:5–7.

In contrast, Dr. Miller opined that some of the stressors which are generally accepted as having an association with SIDS do not involve obstruction of an infant’s airway. For example, he wrote that “[t]here is clear evidence that hyperthermia, whether from an overly warm external environment . . . or fever, is another external stressor[.]” Pet’rs’ Ex. 37 at 6. Dr. Miller continued that this condition is distinguished from the stressor of airflow obstruction seen with prone sleeping, co-sleeping, or blanket use, and “it is unlikely to have its effect through any obstruction of airflow.” *Id.* He further opined that “[t]here is equally clear evidence that [URIs] provoke cytokine responses which have central nervous system [(“CNS”)] actions, not as inflammatory mediators but as modifiers of synaptic activity[.]” *Id.*

Dr. Miller wrote that the majority of SIDS cases involve the presence of two or more stressors. Pet’rs’ Ex. 38 at 5. He explained that the “stressors interact, and their combined effects are likely to be multiplicative or geometric rather than just additive.” *Id.* However, Dr. Miller

<sup>27</sup> Kinney & Thach, *supra* note 13.

<sup>28</sup> *Id.*

<sup>29</sup> Kahn et al., *supra* note 21.

<sup>30</sup> Erwan Stéphan-Blanchard et. al., *Heart Rate Variability in Sleeping Preterm Neonates Exposed to Cool and Warm Thermal Conditions*, 36 PLOS ONE 1 (2011).

emphasized that it “is impossible with present knowledge” to apportion the relative contribution that each stressor would have had. *Id.* at 6. He wrote that “each would represent a substantial contributing factor.” *Id.* Dr. Miller opined that “the most important potential external stressor” for J.J. was the series of vaccinations he received on November 14, 2012. Pet’rs’ Ex. 12 at 4. He asserted that J.J.’s only other risk factors were prematurity and male gender, which are both intrinsic. Dr. Miller testified that there was no evidence of a URI or any other infection. Tr. 82:21–23.

Dr. Gill’s autopsy report identified J.J.’s final diagnosis as SIDS. He then listed additional information which, if not ultimately deemed relevant, was at least initially considered prior to determining the cause of death. Dr. Gill’s list included intrinsic SIDS risk factors, extrinsic risk factors, recent medical history, and test results. Pet’rs’ Ex. 10. Several of the items listed were used to rule out other potential causes of death before SIDS could be considered, e.g., URI history, influenza studies, and cerebrospinal fluid (“CSF”) cultures. *Id.* Other items were identified as SIDS risks factors, such as J.J.’s prematurity and history of co-sleeping. Dr. Gill also listed J.J.’s “recent immunizations”, but there is no indication of what, if any, significance Dr. Gill gave this part of J.J.’s medical history. It is also unclear whether this line item was an example of something that was ruled out as a cause (*see* influenza studies: negative) or identified as a possible contributing risk factor (co-sleeping with twin).

#### **i. Co-Sleeping**

Dr. Miller wrote that “the data on the risks of co-sleeping” largely involve an infant sleeping in the same bed or on a couch with an adult. Pet’rs’ Ex. 38 at 2. He explained that such co-sleeping creates a “hazardous sleeping condition” because it may cause “accidental asphyxiation of the infant when the adult rolls over in his or her sleep and smothers the child, without awakening.” *Id.*

Dr. Miller explained that co-sleeping as a potential external stressor in this case is “almost certainly a red herring, for two reasons[.]” Pet’rs’ Ex. 37 at 6. First, J.J. was sleeping with his approximately equal-sized twin sister in a crib, as opposed to with an adult or older sibling in an adult bed. *Id.* Dr. Miller noted J.J.’s “twin was not large enough to cause asphyxiation should the two of them end up with one on top of the other[.]” and the crib “was large enough for them to be entirely separate, so there was no chance for such an interaction to occur.” Pet’rs’ Ex. 38 at 2. Second, the evidence suggests that his twin sister was removed from the crib before he experienced the event which ultimately led to his death.<sup>31</sup> Pet’rs’ Ex. 37 at 6.

In her testimony, Dr. Folkerth agreed that co-sleeping is “[p]robably not” a risk factor in this case based on Ms. Nunez’s testimony that J.J. and his twin sister slept at opposite ends of the crib. Tr. 177:11–16. Dr. McCusker similarly testified that based on Ms. Nunez’s testimony regarding how the infants were sleeping at opposite ends of their crib, she “would say that this [co-

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<sup>31</sup> Based on the recorded temperature at the time of death, and with the disclaimer that “[e]stimating time of death is admittedly quite imprecise,” Dr. Miller estimated that J.J. died only about an hour prior to the time that his temperature was measured. Pet’rs’ Ex. 38 at 2. Dr. Miller noted that, based on the timeline of events, J.J.’s twin had been removed from the crib well before that time, and thus co-sleeping was not a risk factor contributing to J.J.’s death. *Id.*

sleeping] would not be considered a risk factor.” Tr. 284:13–20. Based on the record as a whole, including Ms. Nunez’s testimony and Respondent’s experts’ ultimate concessions based on that testimony, the undersigned finds that co-sleeping was not a relevant risk factor in this case.

## **ii. Bundling/Use of a Receiving Blanket in the Crib**

Dr. Folkerth provided “soft bedding” and “hyperthermia/overbundling” as examples of exogenous stressors under the Triple Risk Model. Resp’t’s Ex. C at 6. Dr. McCusker also described two ways in which over-bundling is thought to be a risk factor for SIDS. Tr. 206:6–16. She testified that a high ambient temperature can be a risk factor because it can affect the sleep/wake cycle and respiratory rates. Tr. 206:6–11. Additionally, she explained that over-bundling can create a situation where an infant’s startle reflex is compromised, such that if there is a respiratory problem, the infant will not be able to startle himself awake. Tr. 206:14–22. Dr. Miller noted that “[t]here is clear evidence that hyperthermia, whether from an overly warm external environment . . . or fever, is another external stressor[,]” separate from the stressor of airflow obstruction seen with blanket use. Pet’rs’ Ex. 37 at 6.

Dr. McCusker testified that the blanket tucked around J.J.’s legs was not “the equivalent of bundling, but it is not recommended, because it’s considered an increased risk factor for sudden infant death.” Tr. 288:4–6. Dr. McCusker testified that the Pediatric Task Force concluded that “things should not . . . encircle the infant.” Tr. 287:13–14 (citing Resp’t’s Ex. A, Tab 7,<sup>32</sup> ECF No. 38-7). Specifically, Dr. McCusker read the following from the article: “Even if covered by a sheet, it should not be placed under a sleeping infant.” Tr. 286:22–23. Dr. McCusker testified that Ms. Nunez’s “description of having the blanket underneath the child . . . would be considered something that would decrease the startle reflex.” Tr. 208:18–21. She testified that she “didn’t appreciate that when [she] read the notes before, so that’s another sort of add-on” to her list of risk factors in this case. Tr. 206:21–24.

Dr. McCusker’s late addition of the loosely tucked sheet as a risk factor in this case is not persuasive. None of the experts testifying in this case suggested that the crib sheet led to hyperthermia or asphyxiation in J.J. Additionally, the undersigned does not find that the Pediatric Task Force considered a sheet loosely tucked underneath an infant’s legs to be a risk factor separate from hyperthermia-inducing over bundling or mechanical obstruction. In the section that Dr. McCusker referenced, the authors recommend that infants sleep on “a firm sleep surface,” and more specifically, “[a] firm crib mattress, covered by a fitted sheet[.]” Resp’t’s Ex. A, Tab 7 at 3. The sentence referenced by Dr. McCusker during her testimony appears in a paragraph regarding such mattresses, which states in pertinent part:

Pillows or cushions should not be used as substitutes for mattresses or in addition to a mattress. Soft materials or objects such as pillows, quilts, comforters, or sheepskins, even if covered by a sheet, should not be placed under a sleeping infant.

*Id.* By leaving out the context of the sentence that she read, Dr. McCusker did not accurately portray the authors’ concerns regarding the use of a sheet. Dr. McCusker conceded that there were

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<sup>32</sup> Task Force on Sudden Infant Death Syndrome, *SIDS and Other Sleep-Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment*, 128 PEDIATRICS 1030 (2011).

no other soft materials in the crib, other than the sheet. Tr. 287:20–24. Therefore, the undersigned finds that the use of a receiving blanket in this case, based on Ms. Nunez’s description of how she loosely tucked it around J.J.’s legs, was not a relevant risk factor for SIDS.

### iii. Bottle Feeding

Dr. McCusker wrote that breastfeeding and pacifier use are considered “‘protective’ factors in SIDS[,]” because infants with those factors “rouse more easily and more frequently compared to those bottle fed.” Resp’t’s Ex. E at 5 (citing Tabs 4,<sup>33</sup> 16,<sup>34</sup> 17,<sup>35</sup> ECF Nos. 52-4, 53-6, 53-7). In her testimony, Dr. McCusker clarified that “[b]reast feeding is considered to be protective for SIDS[, s]o bottle feeding is considered to be a risk factor.” Tr. 209:5–7. She was unable to answer a question regarding whether a combination of breastfeeding and bottle feeding would change the risk of SIDS. Tr. 309:23–310:5.

The risk associated with bottle feeding is very different than the exogenous stressors such as prone sleeping or co-sleeping, which are associated with the “mechanics of respiration.” Resp’t’s Ex. A at 3. Although breastfeeding’s protective effect was not explained, the literature that Dr. McCusker filed reflects that “[b]reastfeeding is associated with a reduced risk of SIDS[,]” and “[t]he protective effect of breastfeeding increases with exclusivity.” Resp’t’s Ex. A, Tab 7<sup>36</sup> at 5. This article notes that “any breastfeeding has been shown to be more protective against SIDS than no breastfeeding.” *Id.* Therefore, bottle feeding does not appear to affirmatively *contribute to* SIDS, like an unsafe sleeping position does. Instead, breastfeeding serves to help to *protect against* SIDS. In this way, it is more like the intrinsic “risk factors” of prematurity or male gender than exogenous stressors such as a dangerous sleeping environment. Ms. Nunez testified that J.J. was fed with both breastmilk and formula. Tr. 21:20–21. Although exclusive breastfeeding may have a protective effect, the undersigned found nothing in the literature to suggest that SIDS is in any way *caused* by an infant’s having been partially (or exclusively) bottle fed. Because the undersigned is considering potential *causes* of J.J.’s death in this case, the undersigned does not find the fact that J.J. was partially bottle fed to be a significant factor in the analysis.

### iv. Upper Respiratory Infection

#### a. URI as an Exogenous Stressor Generally – Cytokine Production vs. Airway Obstruction

Dr. Miller testified that “one of the risk factors that [has] been statistically highly important” in SIDS cases is having a mild infection. Tr. 53:7–9. He explained that the infection can be either a mild or trivial URI or a gastrointestinal infection. Tr. 53:9–11. In his reports, Dr. Miller wrote that “[a]mong the described external stressors[,] the presence of a URI is prominent[,]” noting that studies have found URIs or other minor infections may be present in anywhere from 20 percent to over 80 percent of SIDS cases. Pet’rs’ Ex. 38 at 4.

<sup>33</sup> Kahn et al., *supra* note 21.

<sup>34</sup> Bert Alm et al., *Breastfeeding and Dummy Use Have a Protective Effect on Sudden Infant Death Syndrome*, 105 ACTA PAEDIATRICA 31 (2016).

<sup>35</sup> Edwin A. Mitchell & Henry F. Kraus, *Sudden Unexpected Death in Infancy: A Historical Perspective*, 51 J. OF PAEDIATRICS AND CHILD HEALTH 108 (2015).

<sup>36</sup> Task Force on Sudden Infant Death Syndrome, *supra* note 32.

Dr. Miller argued that “[t]he mechanism whereby [URIs or other minor] infections increase the risk of a SIDS event . . . is believed to be mediated by cytokines.” *Id.* Dr. Miller explained that the innate immune system produces cytokines, which both “promote the adaptive immune system to react to the pathogens invading the body” and “mobiliz[e] more cells of the intrinsic immune system to attack the pathogens.” *Id.* He opined that “[t]here is . . . clear evidence that [URIs] provoke cytokine responses which have [CNS] actions, not as inflammatory mediators but as modifiers of synaptic activity[.]” Pet’rs’ Ex. 37 at 6. He noted that IL-1, IL-6, and tumor necrosis factor (“TNF”) are among the cytokines produced in response to infection. Pet’rs’ Ex. 38 at 4. Dr. Miller explained that some of these cytokines can cross the blood-brain barrier into CNS tissues. *Id.* (citing Pet’rs’ Ex. 38, Tab D,<sup>37</sup> ECF No. 94-2; Pet’rs’ Ex. 37, Tab M,<sup>38</sup> ECF No. 93-9). Dr. Miller wrote that the cytokines can mediate fever, produce “sick behaviors” such as lethargy, excessive sleepiness, fussiness, crankiness, loss of appetite, and restlessness, and alter sleep patterns. Pet’rs’ Ex. 38 at 4. Dr. Miller also wrote that the cytokine “actions which are thought to lead to SIDS involve the[] suppression of the activity of the serotonergic network[.]” *Id.* This hypothesis is derived “from multiple published experimental animal studies which have examined the functional responses and electrophysiological changes in serotonergic medullary neurons exposed to some of these relevant cytokines.” *Id.* (citing Pet’rs’ Ex. 38, Tabs 5,<sup>39</sup> 6,<sup>40</sup> 7,<sup>41</sup> 8,<sup>42</sup> ECF Nos. 91-10, 92-1, 92-2, 94-3).

Dr. McCusker rejected Dr. Miller’s explanation of how a trivial URI increases the risk of SIDS and wrote that “[c]ytokine production with respiratory or gastrointestinal infections have not been defined as factors” in apneic episodes leading to SIDS. Resp’t’s Ex. E at 6. She further wrote that “[t]here are no studies presented demonstrating that hypercapnia<sup>43</sup> results from cytokine release[.]” *Id.* at 5; *see also* Tr. 200:3–20. Dr. McCusker also testified that she is not aware of any evidence that mild URIs create a risk factor for SIDS by causing a cytokine response in the brainstem. Tr. 207:22–25.

Instead, Dr. McCusker argued that mild infection as a risk factor for SIDS “has to do with [the] compromising of breathing.” Tr. 200:3–4. Specifically, she wrote that URIs “are sufficient to interfere with normal infant respiration and act as a risk factor influencing gas exchange[.]” Resp’t’s Ex. E at 5. Dr. McCusker explained that URIs “result in intermittent obstruction of the

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<sup>37</sup> Steven W. Threlkeld et al., *Ovine Proinflammatory Cytokines Cross the Murine Blood-Brain Barrier by a Common Saturable Transport Mechanism*, 17 NEUROIMMUNOMODULATION 405 (2010).

<sup>38</sup> William A. Banks et al., *Bidirectional Transport of Interleukin-1 Alpha Across the Blood-Brain Barrier*, 23 BRAIN RESEARCH BULLETIN 433 (1989).

<sup>39</sup> Lauritz Stoltenberg et al., *Changes in Apnea and Autoresuscitation in Piglets After Intravenous and Intrathecal Interleukin-1 $\beta$  Injection*, 22 J. PERINAT. MED. 421 (1994).

<sup>40</sup> J. Frederik Frøen et al., *Adverse Effects of Nicotine and Interleukin-1 $\beta$  on Autoresuscitation After Apnea in Piglets: Implications for Sudden Infant Death Syndrome*, 105 PEDIATRICS E52 (2000).

<sup>41</sup> D. Brambilla et al., *Interleukin-1 Inhibits Firing of Serotonergic Neurons in the Dorsal Raphe Nucleus and Enhances GABAergic Inhibitory Post-synaptic Potentials*, 26 EUR. J. NEUROSCI. 1862 (2007).

<sup>42</sup> Alfredo Manfredi et al., *Interleukin-18 Enhances Non-rapid Eye Movement Sleep when Microinjected into the Dorsal Raphe Nucleus and Inhibits Serotonergic Neurons in Vitro*, 18 EUR. J. NEUROSCI. 1041 (2003).

<sup>43</sup> Hypercapnia is an excess of carbon dioxide in the blood. *Dorlands* at 887.

upper airway sufficient to affect the O<sub>2</sub>/CO<sub>2</sub> balance in infants[.]” Resp’t’s Ex. A at 6 (citing Pet’rs’ Ex. 26 at 9,<sup>44</sup> ECF No. 92-4).

Dr. McCusker wrote that “[i]nfants are obligate nose breathers and have relatively small nasal passages and airways.” Resp’t’s Ex. E at 5. Therefore, she explained, “[c]ongestion that occurs with seemingly trivial upper respiratory tract infections results in increases in respiratory effort and distress.” *Id.* Dr. McCusker noted that “[i]ncreases in carbon dioxide levels in affected children have been documented in several studies.” *Id.* However, when discussing the articles that she cited for that assertion, Dr. McCusker acknowledged that the studies were not looking at increases in carbon dioxide levels and that “[t]here is no study that measures CO<sub>2</sub> levels in SIDS patients.” Tr. 275:9–10; *see also* Tr. 273–283.

Dr. McCusker also wrote that “[e]vidence suggests that the central functions of the cytokines IL[-]1 $\beta$ , IL[-]6 and TNF[-] $\alpha$  at times of infection are to promote fever and to affect the sleep architecture by increasing [non-rapid eye movement (“NREM”)] versus [rapid eye movement (“REM”)] sleep resulting in more disturbed sleep with more frequent arousal . . .” Resp’t’s Ex. A at 5 (citing Resp’t’s Ex. A, Tabs 19,<sup>45</sup> 20,<sup>46</sup> 21,<sup>47</sup> ECF Nos. 39-9, 39-10, 40-1). She discussed infant sleep patterns in her supplemental report and wrote that in infants, “NREM sleep is associated with regular heart rate and respiratory patterns[, whereas] REM sleep is more disorganized and considered ‘immature.’” Resp’t’s Ex. E at 4 (citing Resp’t’s Ex. E, Tab 11,<sup>48</sup> ECF No. 53-1). She noted that although “the expression of the circadian rhythm and changes in sleep wake cycles are specific to the infant period, there is no evidence that cytokines act differently in infants[.]” Resp’t’s Ex. E at 4. Therefore, she opined that cytokine increases would actually lead to increased arousal. *Id.*

On cross-examination, Dr. McCusker was asked about the Rognum et al.<sup>49</sup> study, specifically whether mild infection may trigger SIDS by cytokine interaction in a compromised medullary system, and she disagreed with the hypothesis of the paper. Tr. 267:10–18. She then noted that “infection can result in hypercapnia” and that the Rognum et al. paper “actually shows” that “the presence of IL-6 may be related to the response to the infection or the stressor that the baby is undergoing and not be related to actually a mechanistic causality association.” Tr. 268:5–10. Dr. McCusker was asked again to clarify whether the study shows “the elevated IL-6 is related to an infection, but that the elevated IL-6 does not necessarily relate to the impaired respiration.” Tr. 268:11–13. She replied, “No. . . . what they say is that the presence of the IL-6 may be related to the infection or may be related to the increase that – of the CNS in response [to] the stressor.” Tr. 268:14–17. She did not elaborate further. The Rognum et al. study is also supported by the

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<sup>44</sup> Ingvar J. Rognum et al., *Interleukin-6 and the Serotonergic System of the Medulla Oblongata in the Sudden Infant Death Syndrome*, 118 ACTA NEUROPATHOL. 519 (2009).

<sup>45</sup> James M Clinton et al., *Biochemical Regulation of Sleep and Sleep Biomarkers*, 7 J. CLINICAL SLEEP MED. S38 (2011).

<sup>46</sup> Charlene E. Gamaldo et al., *The Sleep-Immunity Relationship*, 30 NEUROLOGIC CLINICS 1313 (2012).

<sup>47</sup> Nicolas Rohleder et al., *Role of Interleukin-6 in Stress, Sleep, and Fatigue*, 1261 ANNALS OF THE N.Y. ACAD. OF SCI. 88 (2012).

<sup>48</sup> Oskar G. Jenni & Mary A. Carskadon, *Sleep Behavior and Sleep Regulation from Infancy through Adolescence: Normative Aspects*, 2 SLEEP MED. CLINICS 321 (2007).

<sup>49</sup> Rognum et al., *supra* note 44.

2009 Kinney et al. study that found that “in infants who die unexpectedly of infection, the given organism may precipitate a lethal cytokine cascade or toxic response.” Pet’rs’ Ex. 37, Tab C at 3.<sup>50</sup>

Dr. McCusker wrote that “[n]asal congestion associated with upper respiratory tract infections can compromise infant respiration and increase carbon dioxide[.]” and that “‘noisy breathing,’ as seen with nasal congestion or obstruction, positively correlates with sleep apnea.” Resp’t’s Ex. E at 6 (citing Resp’t’s Ex. E, Tab 4<sup>51</sup>). When questioned about the basis for her mechanical hypothesis, Dr. McCusker stated that “[i]ncreased CO<sub>2</sub> associated with upper respiratory tract infections in infants is basic pediatrics.” Tr. 274:15–17. She emphasized that an infant with a “stuffed up” nose will use “a lot of respiratory effort,” but there will be “no intake of air,” which usually results in the infant waking up crying or upset. Tr. 200:10–16. She testified that these infants “really do have a lot of difficulty getting their air in because the idea of breathing through the mouth [does not] come naturally to these babies.” Tr. 200:16–20. She added that an infant “making greater respiratory efforts” will have increased metabolic activity, which will also “increase[] the risk of increasing carbon dioxide” in the body. Tr. 201:5–10. Dr. McCusker noted that when a stuffy nose is obstructing the airway, “most of the time, suctioning is all [one] need[s] to do and [the infant’s] oxygen comes right back up.”<sup>52</sup> Tr. 202:17–19.

In response to Dr. McCusker’s arguments, Dr. Miller argued that “[t]here is no support in the literature” for . . . a mechanical hypothesis[.]” of URI as an external stressor, whereby “mechanical obstruction of an infant’s nasal passages by mucus causes hypoxia and leads to SIDS.” Pet’rs’ Ex. 38 at 5. Dr. Miller also disagreed with Dr. McCusker’s assertion that increased cytokine activity would lead to increased arousal. Pet’rs’ Ex. 37 at 5. Dr. Miller opined that “this mechanism might operate in normal infants[.]” whereas in “infants with defective medullary serotonin networks . . . there cannot be a response to cytokines” as described because of the defect. *Id.* He also emphasized that the mechanism described by Dr. McCusker in support of her assertion would not be applicable in this case because infants such as J.J. “have not yet developed sleep regulation by circadian rhythms[.]” and the article studied older children. *Id.* Dr. Miller acknowledged that “over time[,] some cytokines can also stimulate the pituitary-adrenal axis to drive greater production of serotonin in a healthy nervous system[.]” Pet’rs’ Ex. 38 at 6. However, he emphasized that in a developmentally defective nervous system, this stimulation “ought not to be regarded as an argument against the hypothesis that infection or vaccine-induced cytokine responses can suppress the medullary serotonergic network[.]” *Id.*

The role of cytokines stimulated by mild infection is central to Petitioners’ theory in this case, because Dr. Miller compares the cytokine response in mild infection to that of vaccination to explain his theory. The experts drastically diverge in their discussion at this point because Dr. McCusker does not agree with the basis of Dr. Miller’s analogy: the mechanism by which a mild

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<sup>50</sup> Kinney & Thach, *supra* note 13.

<sup>51</sup> Kahn et al., *supra* note 21.

<sup>52</sup> Dr. McCusker testified that “[i]n more severe cases,” if an infant’s carbon dioxide level is “very, very high,” they may “need assisted ventilation in order to get through that infection.” Tr. 202:19–24. Dr. McCusker discussed bronchiolitis, where an infant’s upper and lower airways become obstructed, and noted that even in such severe cases, “first-line management of bronchiolitis is upper airway suctioning.” Tr. 203:18–22.

infection can increase the risk of SIDS. Dr. Miller points to the Rognum et al.<sup>53</sup> study which “provides evidence for aberrant interactions in SIDS infants between IL-6 and the arcuate nucleus, a key medullary 5-HT related region . . . potentially induced by the combined effect of prone position and mild infection.” Pet’rs’ Ex 26 at 9. He then uses that same mechanism to argue that a vaccine-initiated immune response is by its very nature similar to the immune response prompted by an infection and, consequently, “[the mechanism] applies to all vaccines.” Tr. at 89:23.

**b. URI as an Exogenous Stressor in this Case**

Dr. Miller wrote that Petitioners’ descriptions of J.J. and his twin having “‘runny noses and a productive’ cough” at the time of their visit to the pediatrician on November 14, 2012, “suggest that J.J. had a URI[.]” Pet’rs’ Ex. 38 at 3. However, he noted that references to “runny noses and productive coughs” come from Petitioners’ affidavits, which “were put together months after the infant’s death[.]” Pet’rs’ Ex. 37 at 3.

Dr. Miller highlighted that neither the pediatrician’s note from the evening of November 14, 2012, nor the November 15, 2012 EMS and emergency department notes contain any indication that Petitioners described a runny nose or recent URI symptoms at the time of J.J.’s death. Pet’rs’ Ex. 37 at 3. Dr. Miller noted in his testimony that the pediatrician’s note contains “a lot of specifics . . . in terms of physical examination that are mentioned that are all normal findings, including . . . that there was no nasal discharge.” Tr. 32:14–16. He also emphasized that the records from November 15, 2012, reflect only that J.J. was “cranky” after his vaccinations. Pet’rs’ Ex. 37 at 4. Dr. Miller testified that he “tend[s] to go with medical records rather than parent recollections” when the two conflict. Tr. 82:15–17. Therefore, Dr. Miller stated that “[f]or the purposes of analyzing potential risk factors” in the Triple Risk Model, he “cannot agree that there is any medical evidence [of] an URI in [J.J.] on the day before his death[.]” Pet’rs’ Ex. 37 at 4; *see also* Tr. 82:21–23.

Dr. Miller conceded that Dr. Gill’s autopsy report listed “recent upper respiratory infection” under the “final diagnoses” section but noted that “recent immunizations” is noted on the same list. Pet’rs’ Ex. 37 at 3–4. Therefore, Dr. Miller opined that, “[i]f the ME report is to be regarded . . . as reliable as to the history of a recent URI as a contributing factor for SIDS . . . , [then the inclusion of] ‘[r]ecent immunizations’ directly under the diagnosis of the URI[ is] presumably equally important as a potential contributor to death in this case.” *Id.* at 4. Dr. Miller opined that if there were medical evidence of a mild infection in this case, “it would be an additional risk factor.” Tr. 120:12–15. Dr. Miller opined that if J.J. did have a mild URI at the time of vaccination, it may have “further increase[d] the risk of a SIDS event over the risk of exposure to either stressor[, i.e., mild URI or vaccination,] alone.” Pet’rs’ Ex. 38 at 6. However, he testified that such a finding would not change his analysis that the vaccines were still a substantial contributing factor for the death. Tr. 120:21–23.

Dr. McCusker discussed URI as a risk factor for SIDS in this case without substantially addressing the contradiction between the medical records and Petitioners’ affidavits. In both of her reports, Dr. McCusker wrote that J.J.’s “parents reported nasal congestion, runny nose and cough on the day and evening of November 14, 2012.” Resp’t’s Ex. A at 1; Resp’t’s Ex. E at 1.

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<sup>53</sup> Rognum et al., *supra* note 44.

In her first report, she opined that J.J. “had symptoms of an upper respiratory tract infection[,]” among his risk factors for SIDS. Resp’t’s Ex. A at 3. In her second report, Dr. McCusker listed “upper respiratory tract infection (per his parents)[]” as a risk factor in this case. Resp’t’s Ex. E at 5. In her testimony, Dr. McCusker indicated that she was “[p]erhaps . . . referring to the congestion associated with the upper respiratory tract infection in October” when she included congestion in her summary of symptoms on the evening of November 14, 2012. Tr. 262:15–23. She conceded that there was no parental report nasal congestion on November 14, 2012. Tr. 263:1–4. However, she nonetheless testified that “[t]he presence of the upper respiratory tract infection would be considered a risk factor” in this case. Tr. 208:15–17. With regard to the absence of notation in the medical records regarding URI symptoms on November 14, 2012, Dr. McCusker testified that “on the balance of probabilities, in this situation, when the parents are clearly giving statements related to runny nose and cough at the time of the vaccination, then you have to feel that there was probably some runny nose and cough.” Tr. 265:15–19. Dr. Folkerth summarized in her report that the father reported “runny noses and productive coughs,” but she acknowledged that “the doctor’s note for that visit describes no fever or cough or other abnormality.” Resp’t’s Ex. C at 3. She did not list URI among the risk factors for SIDS in this case. *See id.* at 7.

Discussing the “final diagnoses” section of the autopsy report, Dr. Folkerth was asked about the significance of the nine listed items underneath “sudden unexpected death in infant.” Tr. 169:16–21. Dr. Folkerth agreed that it is “[g]enerally true” that each listed item under the final diagnosis is relevant to the cause of death. Tr. 169:19–22. However, she testified that the office where the autopsy was performed, which is the same office where she now works, receives all the medical records of an infant prior to autopsy. Tr. 172:19–20. Therefore, she opined that the medical examiner, Dr. Gill, “was listing some of the historical [data]—the things that were known about the baby’s history as things to be ruled out as possible historical significance to the child,” and not necessarily items which he felt were related to the SIDS diagnosis. Tr. 170:4–7.

There is contradicting evidence in the record regarding whether J.J. was exhibiting symptoms consistent with a URI on the day of his death. The medical records do not document any type of infection or note that J.J. suffered any symptoms. However, the affidavits in this case state that J.J. was suffering from runny nose and cough. Additionally, Ms. Nunez testified that on the day of J.J.’s four-month pediatrician appointment, she was not concerned by his symptoms. Tr. 24:19–21. She stated that J.J.’s nose was “no longer stuffy” as it had been in October when he suffered from congestion, and his cough “was getting better.”<sup>54</sup> Tr. 22:18, 24:16. She explained that his nose was “just runny” with no congestion, and there was only a “very light, clear, like mucus or just clear from the allergies.” Tr. 22:19–21. Based on the medical record and the testimony provided by Ms. Nunez, the undersigned finds that it is more likely than not that J.J. had a runny nose but was not suffering from a URI on the evening that he received the vaccines at issue in this case.

### **C. Vaccination as a Risk Factor for SIDS**

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<sup>54</sup> Furthermore, she testified that she was instructed about how to decongest J.J.’s nostrils with saline when he had a stuffy nose in the beginning of October 2012. Tr. 23. Therefore, it is most plausible that if J.J. had congestion on the evening when he received his vaccines, Ms. Nunez would have been able to remedy the stuffiness such that J.J.’s airway would not be obstructed.

Dr. Miller wrote that he has seen “well over a dozen” cases of SIDS death within 48 hours of vaccination as part of his regular work as a neuropathologist and as an expert in the Vaccine Program. Pet’rs’ Ex. 12 at 5. Dr. Miller explained that “the peak age for SIDS is between 2 and 4 months of post-natal age, corresponding to ages at which infants now receive their first and second rounds of multiple vaccinations.” Pet’rs’ Ex. 12 at 5; *see also* Pet’rs’ Ex. 15<sup>55</sup> at 2 (“Ninety percent of SIDS occurs in the first 6 months of life, with a peak at 2–4 months[.]”). He noted that such a correlation “raises a suspicion that vaccinations may trigger SIDS[.]” a suspicion which he emphasized is recognized in some medical literature. Pet’rs’ Ex. 12 at 5 (citing Pet’rs’ Exs. 30–33,<sup>56</sup> ECF Nos. 92-8, 92-9, 92-10, 93-1). Dr. Miller acknowledged that no single piece of medical literature sets forth his theory of causation. Tr. 96:7–10. Dr. Miller testified that “Dr. Kinney has never evaluated vaccinations one way or the other.” Tr. 94:23–24.

Dr. Folkerth testified that she has never seen a case where she would attribute a death to vaccination, other than acute immediate reactions. Tr. 173:2–15. Dr. McCusker testified that she does not believe that any vaccine, under any circumstance, could result in SIDS. Tr. 332:16–20.

### 1. Epidemiological Studies

The 1991 Adverse Effects of Pertussis and Rubella Report concludes that “evidence does not indicate a causal relation[ship] between DPT vaccine and SIDS.” Pet’rs’ Ex. 34 at 18 (filed on compact disk; ECF No. 22).<sup>57</sup> The 2012 Adverse Effects of Vaccines Report, however, held that “evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and ITP.” Pet’rs’ Ex. 35 at 62 (filed on compact disk; ECF No. 22).<sup>58</sup>

In the 2000 article by Jonville-Bera et al.,<sup>59</sup> the authors “conducted a multicentre case-control study in the 28 French ‘SIDS Centers.’” Resp’t’s Ex. A, Tab 25 at 1, ECF No. 40-5. The authors selected 114 cases based on deaths labeled as a SIDS death of an infant between 30 and 90 days old. *Id.* The study’s authors selected 341 living controls (approximately three per case of SIDS), who were “matched for sex [and] gestational age[.]” *Id.* The controls were also “born immediately after the victim in the same maternity unit.” *Id.* The study’s authors found that “vaccination does not constitute a risk factor for early SIDS[.]” *Id.* at 4. However, they noted

<sup>55</sup> Kinney et al., *supra* note 17.

<sup>56</sup> Pet’rs’ Ex. 30, Rüdiger von Kries et al., *Sudden and Unexpected Deaths After the Administration of Hexavalent Vaccines (Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B, Haemophilus Influenzae Type b): is there a signal?*, 164 Eur. J. Pediatrics 61 (2005); Pet’rs’ Ex. 31, B. Zinka et al., *Letter to the Editor: Unexplained Cases of Sudden Infant Death Shortly After Hexavalent Vaccination*, 24 VACCINE 5779 (2006); Pet’rs’ Ex. 32, Giulia Ottaviani et al., *Sudden Infant Death Syndrome (SIDS) Shortly After Hexavalent Vaccination: Another Pathology in Suspected SIDS?*, 448 VIRCHOWS ARCHIV 100 (2006); Pet’rs’ Ex. 33, Giuseppe Traversa et al., *Sudden Unexpected Deaths and Vaccinations During the First Two Years of Life in Italy: A Case Series Study*, 6 PLOS ONE e16363 (2011).

<sup>57</sup> INSTITUTE OF MEDICINE, ADVERSE EFFECTS OF PERTUSSIS & RUBELLA VACCINES 125–43 (Christopher P. Howson et al. eds., National Academy Press 1991).

<sup>58</sup> INSTITUTE OF MEDICINE, ADVERSE EFFECTS OF VACCINES. EVIDENCE AND CAUSALITY 581–82 (Kathleen Stratton et al. eds., National Academy Press 2011).

<sup>59</sup> Annie-Pierre Jonville-Bera et al., *Sudden Unexpected Death in Infants Under 3 Months of Age and Vaccination Status—a Case-control Study*, 51 BRITISH J. CLINICAL PHARMACOLOGY 271 (2000).

several biases which “might explain a failure to demonstrate a risk[,]” including a selection bias affecting the representativeness of the cases. *Id.* at 5. Dr. McCusker wrote that the authors “found that vaccination was not an independent risk factor for SIDS.” Resp’t’s Ex. A at 7.

The 2007 article by Vennemann et al.<sup>60</sup> examined “[n]ine case-control[] studies” which examined a potential association between immunization and SIDS. Resp’t’s Ex. A, Tab 24 at 1, ECF No. 40-4. The authors found that “[i]mmunisations are associated with a halving of the risk of SIDS[]” and that they should thus “be part of the SIDS prevention campaigns.” *Id.* The authors noted that “[t]here are biological reasons why this association may be causal, but other factors, such as the healthy vaccine effect, may be important.” *Id.*

The 2010 paper authored by Traversa et al.<sup>61</sup> studied “whether the immunisation with hexavalent vaccines increased the short[-]term risk of [sudden unexplained death] in infants” in Italy. Pet’rs’ Ex. 33 at 1. The authors considered a population of “around 3 million infants vaccinated in Italy” between 1999 and 2004, of which “1.5 million received hexavalent vaccines[.]” *Id.* For that population, events of sudden infant death were identified using death certificates, and vaccination history was “retrieved from immunisation registries.” *Id.* A case series design was utilized, which focused on varying intervals of risk periods between zero and fourteen days after vaccination. *Id.* The authors concluded that the relative risks of sudden unexplained death “for any vaccines and any risk periods, even when greater than 1, were almost an order of magnitude lower than the estimates” of another study conducted in Germany.<sup>62</sup> *Id.* They found that “[t]he limited increase in [relative risks] found in Italy appears confined to the first dose and may be partly explained by a residual uncontrolled confounding effect of age.” *Id.*

Dr. Miller emphasized that there was “a statistically significant increased risk of sudden death” following the first doses of several vaccinations, although he acknowledged that the authors did not find such a risk after second doses. Tr. 79:12–14. In contrast, Dr. McCusker emphasized the authors’ acknowledged limitation of “the confounding effect of age[.]” Resp’t’s Ex. A at 7. Dr. McCusker also noted that the “association was not seen in older infants with subsequent vaccination.” *Id.* Furthermore, she noted that the authors of that study, “as in others,” found a lower immunization rate among sudden unexplained death cases when compared with controls, which she opined “support[s] the concept of the ‘healthy vaccinee effect’ where vaccination appears to reduce the risk of SID[S].” *Id.*

Dr. McCusker used many of the studies to support her position that “there is no evidence for a role of vaccination in SIDS in the epidemiologic literature.” *Id.* at 9. She wrote that “[w]ell designed publications . . . increase the strength of evidence against a causal association for SIDS and vaccines providing strong epidemiological evidence for temporal association only.” *Id.* at 7

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<sup>60</sup> M.M.T. Vennemann et al., *Sudden Infant Death Syndrome: No Increased Risk After Immunisation*, 25 VACCINE 336 (2007).

<sup>61</sup> Traversa et al., *supra* note 56.

<sup>62</sup> The referenced study was filed as Petitioners’ Exhibit 30 and will be discussed below.

(citing Resp't's Ex. A, Tabs 24,<sup>63</sup> 28;<sup>64</sup> Pet'rs' Ex 33;<sup>65</sup>). She wrote that those "studies were designed to be sufficiently powered to evaluate associations for rare events." *Id.* She did not elaborate further on what made the studies well designed or why she felt they were "sufficiently powered." *See id.*

Dr. McCusker wrote that the findings in the Toro et al.<sup>66</sup> study "suggest[] that vaccination was a protective measure for children at risk for SIDS[]" because the incidence of SIDS lowered when children were vaccinated. Resp't's Ex. A at 7 (citing Resp't's Ex. A, Tab 26, ECF No. 40-6). Dr. McCusker also referred to the article by Moro et al.,<sup>67</sup> which looked at "the mortality data in the [Vaccine Adverse Event Reporting System ("VAERS")] dataset." *Id.* (citing Resp't's Ex. A, Tab 27, ECF No. 40-7). She wrote that the authors "found no difference in frequency or patterns of SIDS compared with the expected frequency in the population." *Id.*

Dr. Miller testified that there have been "more than several" epidemiological studies which have looked at the potential role of vaccination in sudden infant death and noted that some have found an increased incidence and some have not. Tr. 79:19–22. Dr. Miller also acknowledged that some medical literature reflects no relationship between vaccines and SIDS. Pet'rs' Ex. 12 at 5 (citing Pet'rs' Exs. 34,<sup>68</sup> 35<sup>69</sup>). However, Dr. Miller opined that "none of the epidemiological studies on this question have been appropriately done with quality neuropathological examinations[, which are] the necessary foundation for any quality study." *Id.* Dr. Miller wrote that he has previously "detailed and testified as to the inadequacies of virtually all of the epidemiological studies" which have considered possible relationships between vaccinations and SIDS. Pet'rs' Ex. 37 at 8. He declined to "consider any of [the studies] in detail" in his report, *id.*, and stated that "[m]ultiple published re-analyses of epidemiological studies which originally claimed to show no statistically significant relationship between vaccinations and SIDS have shown major defects in how those studies were constructed and/or analyzed[,]" but he averred that there "are too many to cite[.]" Pet'rs' Ex. 12 at 5. Dr. Miller concluded that none of the studies "are convincing that there is no relationship between vaccinations and SIDS in . . . those [infants] with defective medullary 5-HT networks," which is central to his causation theory. Pet'rs' Ex. 37 at 8. Dr. Miller noted that "no test exists in living children[]" for such a vulnerability, which limited the ability to study it adequately. *Id.*

The 2012 paper by Kuhnert et al.<sup>70</sup> reexamined three previously published case-control studies. Resp't's Ex. A, Tab 28. The three reexamined studies were: the German study on sudden infant death (GeSID) by Vennemann et al.; the Confidential Enquiry into Still Births and Deaths

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<sup>63</sup> Vennemann et al., *supra* note 60.

<sup>64</sup> Kuhnert et al., *Reanalyses of Case-control Studies Examining the Temporal Association Between Sudden Infant Death Syndrome and Vaccination*, 30 VACCINE 2349 (2012).

<sup>65</sup> Traversa et al., *supra* note 56.

<sup>66</sup> Klára Toro et al., *Change in Immunisation Schedule and Sudden Infant Death Syndrome in Hungary*, 42 FEMS IMMUNOLOGY AND MED. MICROBIOLOGY 119 (2004).

<sup>67</sup> Pedro L. Moro et al., *Deaths reported to the Vaccine Adverse Event Reporting System (VAERS), United States, 1997–2013*, 61 VACCINES 980 (2015).

<sup>68</sup> Howson et al. (eds.), *supra* note 57.

<sup>69</sup> Stratton et al. (eds.), *supra* note 58.

<sup>70</sup> Kuhnert et al., *supra* note 64.

in Infancy (CESDI) study by Fleming et al.; and the New Zealand Cot Death (NZCD) study by Mitchell et al. Dr. McCusker described the Kuhnert report as “one of the more definitive studies.” Tr. 245:25–246:1. Dr. McCusker also noted that the authors of this study found that “the healthy vaccine effect” discussed in the Vennemann et al. paper “was basically an overcall.” Tr. 249:7–8. Ultimately, the Kuhnert authors did not find an association between vaccination and sudden infant death and she acknowledged that “there wasn’t a benefit to vaccination” either. Tr. 249:7–10.

Dr. Miller testified that the Kuhnert et al. study has several issues, including use of non-vaccinated individuals as controls. Tr. 351:14–352:7. He also opined that “when you start manipulating data over and over again,” as he posited was done in that study, “all sorts of biases that just distort [the] study” are introduced. Tr. 353:12–13. He opined that based on that manipulation, he does not view the study as “statistically reliable.” Tr. 353:14–15.

## 2. Case Reports

Dr. Miller briefly reviewed several articles where there was a temporal correlation found between vaccination and SIDS. Tr. 77:10–79:1 (discussing Pet’rs’ Exs. 30,<sup>71</sup> 31,<sup>72</sup> 32<sup>73</sup>). He did not draw any specific conclusions from these studies but stated that the authors in one study were “looking for a signal . . . [that there was] something happening after vaccination that led to SIDS...”; in another, authors were “concern[ed] that this new vaccine schedule and this new combination of vaccines might be dangerous . . .” Tr. 77:19–22, 78:3–10.

Dr. McCusker testified that “a case report is the lowest strength of evidence” in epidemiology. Tr. 244:7–9. She explained that a case series then groups together five or six case reports “all with the same or similar story” and suggests that “maybe there’s something going on.” Tr. 244:11–14. She continued that “in order to really define whether or not there . . . may be an association that’s greater than just time, you need to design a better study.” Tr. 17–21. Dr. McCusker testified that the “best study” is a “randomized control trial [where] you enroll all children that are born and half get vaccinated and the other half don’t[, and then] you follow them forward and you see if there’s any difference in sudden infant death between the two groups.” Tr. 244:22–245:3. However, such a study cannot be ethically conducted “because there are so many benefits associated with vaccination.” Tr. 245:4–5. Dr. McCusker noted that cohort studies or case control studies are the next best options. Tr. 245:8–9.

Dr. McCusker discussed the Moro et al. article that analyzes deaths reported to the VAERS, including “child reports with available death certificates/autopsy reports [that listed] sudden infant death syndrome (n = 544 [44%]).” Tr. 251:9–21 (citing Resp’t’s Ex A, Tab 27<sup>74</sup> at 1). She testified that Moro “found that there was no concerning pattern noted amongst the death reports with respect to vaccinations in SIDS in that the frequency of death in the reported group was not different from the frequency in the general population.” Tr. 251:25–252:4. Dr. McCusker acknowledged that

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<sup>71</sup> Kries et al., *supra* note 56.

<sup>72</sup> Zinka et al., *supra* note 56.

<sup>73</sup> Ottaviani et al., *supra* note 56. Dr. Miller conceded that the Ottovani case report, where an infant died within an hour or so after vaccination, would fall outside of a timeline that he would consider suspicious of causation. Tr. 111:6–11.

<sup>74</sup> Moro et al., *supra* note 67.

VAERS relies on self-reporting but testified that “since the event in this situation is death, you would expect it to be more often reported rather than not.” Tr. 252:8–10.

Regarding an article by Zinka et al.,<sup>75</sup> Dr. McCusker wrote that “5 autopsies in children who died within 1–2 days of vaccination showed a significant element of brain oedema [sic] associated with cellular infiltration of unknown etiology and in one case necrosis of the cerebellum.” Resp’t’s Ex. A at 6 (citing Pet’rs’ Ex. 31). She explained that “the authors noted that this would represent a significant increase (13 fold) in SIDS deaths in the local region in Germany” if the deaths were classified as SIDS. *Id.* at 6–7. Dr. McCusker explained that the authors of that study “suggested [the need to conduct] a study to examine, in a larger population, the frequency of SIDS and hexavalent vaccination.” *Id.* She noted that a 2007 “large case[-]control study also from Germany showed no association with vaccination and SIDS.” *Id.* at 7 (citing Resp’t’s Ex. A, Tab 24<sup>76</sup>).

#### **D. Proposed Biological Mechanism for a Causal Role of Vaccines in SIDS**

As was articulated in *Boatmon*, a previous SIDS claim in the Program, “[t]he question arises as whether the cytokine response stimulated by vaccination can have the same effect as a mild or trivial infection in a baby who presumably has a defect in the medullary 5-HT system.” *Boatmon*, 2017 WL 3432329, at \*12.

Dr. Miller began to answer this question by concluding that “the same mechanisms can be presumed to be involved[]” in vaccination-related SIDS as are involved in infection-related SIDS. Pet’rs’ Ex. 38 at 4. He explained that vaccinations “provoke a reaction from the innate immune system, just as if they were an actual infection.” *Id.* Dr. Miller emphasized that vaccinations “provoke cytokine production[;] that’s what they’re designed to do.” Tr. 85:6–7. He noted that “it’s irrelevant” in terms of the type of vaccine received, but he explained that data suggest that “[i]t may be relevant in terms of how many vaccines” are received, because there may be a “more vigorous . . . cytokine response” when more vaccines are added. Tr. 119:25–120:6. Dr. Miller stressed that a minor viral URI “elicit[s] the same cytokine response as a vaccination.” Pet’rs’ Ex. 12 at 5 (citing Pet’rs’ Ex. 29,<sup>77</sup> ECF No. 92-7).

Dr. Miller testified that when the immune system detects “what it perceives as a foreign antigen,” multiple cytokines are produced. Tr. 67:23–68:1. Dr. Miller explained that therefore “vaccinations lead, inevitably and as a natural event, to the production of circulating cytokines including IL[-]2, IL-6, and IL[-]1 $\beta$  (and likely others)[.]” Pet’rs’ Ex. 37 at 6. He explained that “these cytokines can cross from the blood into the brain, where they can have synaptic modulatory effects which produce multiple physiological changes, including fever and suppression of medullary 5-HT activity.” *Id.* Dr. Miller emphasized that “in an infant with an already defective 5[-H]T system,” the suppression of medullary 5-HT activity caused by those cytokines “may be enough in any given situation of apnea or hypercapnia to produce a failure of arousal and increased respiration, leading then to death.” *Id.* at 6–7.

<sup>75</sup> Zinka et al., *supra* note 56.

<sup>76</sup> Vennemann et al., *supra* note 60.

<sup>77</sup> Ashild Vege & Torleiv Ole Rognum, *Sudden infant death syndrome, infection and inflammatory responses*, 42 FEMS IMMUNOLOGY MED. MICROBIOLOGY 3 (2004).

Dr. Miller wrote that one recent study on the “potential relationships between SIDS, sleep, and infantile febrile seizures has re-emphasized the importance of the defects in the medullary serotonergic system and network[.]” Pet’rs’ Ex. 12 at 5 (citing Pet’rs’ Ex. 36,<sup>78</sup> ECF No. 93-2). That study looked at “factors which interact with this underlying defect” to produce either SIDS or sudden death after a seizure, including “fever, high body temperature from environmental causes, maternal smoking, prematurity, male sex, [URIs], and sleep position[.]” *Id.* Dr. Miller noted that the “study does not mention, and does not deal with, the issue of vaccinations,” but he opined that “it is clear . . . that the elevations in cytokines produced by vaccinations act through the same pathways, and often the same molecules, as several of the quoted risk factors, especially infections.” *Id.* Therefore, Dr. Miller opined that it is “probable that vaccinations elicit cytokine production which can suppress arousal and breathing responses, and that this suppression can cross a fatal threshold when the infant in question is vulnerable because of an already defective medullary serotonin system.” *Id.*

### 1. Evidence Regarding Cytokines in the Brain

Dr. Miller acknowledged the role of some cytokines as neuromodulators but argued that cytokines “can get to [parts of the brain] directly by some mechanisms or may act at the interface of the brain with the rest of the world, which is called the blood-brain barrier.” Tr. at 56:2–6. Dr. Miller then stated that cytokines IL-1 $\beta$  and IL-6 have “been found to be elevated in post-mortem specimens from SIDS patients.” Pet’rs’ Ex. 12 at 4 (citing Pet’rs’ Exs. 25,<sup>79</sup> 26,<sup>80</sup> 27,<sup>81</sup> ECF Nos. 92-3, 92-4, 92-5).

Dr. McCusker responded that cytokines “that are found in the CNS are more likely than not intrinsically produced by the CNS, and [are] not coming from the peripheral functioning immune system.” Tr. 334:19–22. She explained that “normal brains under normal physiologic conditions produce cytokines,” which are referred to as neurokines “because they are operating as signaling molecules from neuron to neuron.” Tr. 195:18–23. Dr. McCusker wrote that cytokines are released by microglial cells in the brain, and production can increase when those cells are exposed to psychological or other stressors, such as acute brain injury or neurodegeneration. Resp’t’s Ex. A at 4 (citing Resp’t’s Ex. A, Tabs 13,<sup>82</sup> 15,<sup>83</sup> 16<sup>84</sup>). Dr. McCusker testified that “if our bodies would allow cytokines to sort of flood into the CNS, we would end up with a lot of trouble.” Tr. 336:8–10.

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<sup>78</sup> Toke Hoppenbrouwers, *Sudden Infant Death Syndrome, Sleep, and Seizures*, 30 J. of Child Neurology 904 (2015).

<sup>79</sup> Hazim Kadhim et al., *Distinct Cytokine Profile in SIDS Brain. A Common Denominator in a Multifactorial Syndrome?*, 61 NEUROLOGY 1256 (2003).

<sup>80</sup> Rognum et al., *supra* note 44.

<sup>81</sup> Hazim Kadhim et al., *Interleukin-2 as a Neuromodulator Possibly Implicated in the Physiopathology of Sudden Infant Death Syndrome*, 480 NEUROSCIENCE LETTERS 122 (2010).

<sup>82</sup> Noga Ron-Harel et al., *Brain Homeostasis is Maintained by “Danger” Signals Stimulating a Supportive Immune Response Within the Brain’s Borders*, 25 BRAIN, BEHAVIOR, AND IMMUNITY 1036 (2011).

<sup>83</sup> Hugo O. Besedovsky & Adrianna del Rey, *Central and Peripheral Cytokines Mediate Immune-brain Connectivity*, 36 NEUROCHEMICAL RES. 1 (2011).

<sup>84</sup> Yun Su et al., *Predator Exposure-induced Cerebral Interleukins are Modulated Heterogeneously by Behavioral Asymmetry*, 135 IMMUNOLOGY LETTERS 158 (2011).

**i. Cytokines Constitutively Expressed in the Brain**

Dr. Miller described how cytokines in the brain “have depressive effects on the serotonin system in the medulla and can suppress whatever arousal mechanisms might remain in an infant with a maldeveloped or damaged medulla.” Pet’rs’ Ex. 12 at 4.

Dr. McCusker pointed out that “cytokines have also been shown to be constitutively expressed by cells of the brain and play distinct roles in normal brain homeostasis[.]” Resp’t’s Ex. A at 4. She opined that those cytokines “are not considered ‘proinflammatory,’” like those in the peripheral immune system. *Id.* She continued that “[n]ormal brain function requires [the] release of cytokines[.]” which she explained “play essential roles in neuroprotection and neuromodulation.” *Id.* (citing Resp’t’s Ex. A, Tab 14,<sup>85</sup> ECF No. 39-4). Citing an article authored by Dr. Kinney, Dr. McCusker opined that “the presence of the increased cytokines [in the brain of infants who died of SIDS] is considered to occur in response to the inciting event of hypoxia/hypercapnia[,] rather than represent[ing] an element etiologically linked to the respiratory failure in the vulnerable child.” *Id.* at 5.

In her reports, Dr. McCusker also wrote that “there is significant evidence in the medical literature that cytokines play important roles in both maint[aining] homeostasis in the brain and in alerting the system to potential danger.” *Id.* She explained that “in children experiencing a premortal event, cytokines involved in neuroprotection would be released in an attempt to ‘save’ the system.” *Id.* at 5–6. Therefore, she opined that the “differences in IL[-]6 and IL[-]6R levels seen in SIDS children are likely a marker of the acute brain injury prior to death[,] and the presence of cytokines in the brain of SID[S] patients represent[s] normal physiologic responses to the stressors associated with their terminal events.” *Id.* at 6.

Dr. McCusker agreed with Respondent’s counsel that the articles filed by Petitioners “look at more the expression of a cytokine as opposed to the effect of the cytokine.” Tr. 242:14–18. She reiterated that the function of cytokines in the CNS is different than their function in the peripheral body. Tr. 242:23–25. She testified that IL-1 $\beta$  is involved in sleep and arousal cycles and that without IL-6, “you don’t lay down long-term memories properly.” Tr. 242:19–23.

Dr. McCusker admitted that she could not answer a question regarding how many cytokines would be necessary to affect the brain of an infant with a defect in the medullary serotonergic network, as opposed to a normal brain. Tr. 333:16–21. Dr. McCusker testified that she was assuming that the brain of an infant who dies from SIDS is able to properly regulate cytokines, as a baseline. Tr. 336:18–20. She testified that she has “no evidence that says that [such brains] operate differently, with the exception that the receptor changes that are found in the IL-6 system do[] suggest that they are less sensitive to the presence of the cytokines.” Tr. 336:22–337:1. Dr. McCusker testified that this type of intrinsic defect would work against the idea of cytokines overwhelming the brain, because such a brain would be less sensitive to the presence of cytokines. Tr. 337:2–9.

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<sup>85</sup> Shamsudheen Moidunny et al., *Interleukin-6-type Cytokines in Neuroprotection and Neuromodulation: Oncostatin M, but not Leukemia Inhibitory Factor, Requires Neuronal Adenosine A1 Receptor Function*, 114 J. OF NEUROCHEMISTRY 1667 (2010).

## ii. Circulating Cytokines

Dr. McCusker testified that a person does not “have massive amounts of circulating cytokines, except in the case of a cytokine storm.” Tr. 192:24–193:1. Cytokine storm is “the classic example of cytokines going rogue,” where the body experiences “uncontrolled cytokine release.” Tr. 189:16–20. Dr. McCusker testified that this results in “multi-system effects,” such as “kidney shutdown, . . . liver failure, . . . failure of the bone marrow to produce white blood cells and red blood cells[,] or pulmonary compromise because of pulmonary inflammation.” Tr. 190:2–8. However, Dr. McCusker testified that “even in a cytokine storm, the effects of this massive release of cytokines on the CNS is actually much less than in the rest of the body.” Tr. 190:9–11. She testified that “most of the effects of this massive release of cytokines are seen in the systemic immune system, systemic body, and not as much in the CNS.” Tr. 190:16–18. Dr. McCusker explained that “people can die of cytokine storm,” and “over three or four days you see their immune systems just go crazy and they’ll die within a week or two if you can’t shut down the system.” Tr. 109:19–24.

Dr. McCusker contrasted the multisystem failure that occurs during a cytokine storm to a “normal coordinated immune response.” Tr. 190:25–191:1. Dr. McCusker wrote that cytokine production in the body is subject to “diurnal variations” but acknowledged that “[v]accination is predicted to activate immune responses in part through cytokine up[-]regulation.” Resp’t’s Ex. A at 4 (citing Resp’t’s Ex. A, Tab 10,<sup>86</sup> ECF No. 38-10). During this response, Dr. McCusker continued, the peripheral immune system produces and releases cytokines, “but there is no evidence to suggest that the levels are sufficient to influence the brain . . . .” *Id.* She testified that cytokines “have a very short half[-]life” and do not “live very long from the time that they’re released.” Tr. 192:3–5. Dr. McCusker explained that they “are rapidly either taken up by a cell which has a receptor[] and/or they are degraded by protease in the serum.” Tr. 192:6–8. Additionally, Dr. McCusker testified that “as cytokines start to go up, so does the production of the off switches,” or the “decoy receptor[s],” which she explained “basically pull[] away and trap[]” the cytokines “so that you do not get excessive inflammation.” Tr. 192:9–18. Dr. McCusker concluded that “to get from the thigh or the draining lymph node and to put those cytokines as implicated in a death in the CNS is just biologically not tenable, given our current understanding of cytokine biology.” Tr. 335:2–6.

## iii. Crossing the Blood-Brain Barrier

Dr. Miller testified that “there are at least two ways, and maybe more,” that cytokines can enter the brain. Tr. 112:21–24. First, he explained that “[t]here are areas in the brain which lack a blood-brain barrier normally,” such that “circulating molecules can cross into the brain just by diffusion.” Tr. 112:24–113:8. Alternatively, “there is an active transport system” where cytokines in the blood “come up against brain endothelial cells and can be grabbed and transported into the central nervous system across the blood-brain barrier.” Tr. 113:12–16. He testified that “it’s an energy-dependent process and it’s a saturable process.” Tr. 113:16–17. Dr. Miller described a paper by Banks et al.,<sup>87</sup> which “demonstrated that radiolabeled IL[-]1 $\alpha$  which was] injected

<sup>86</sup> Aroon D. Hingorani et al., *Acute Systemic Inflammation Impairs Endothelium-dependent Dilatation in Humans*, 102 CIRCULATION 994 (2000).

<sup>87</sup> Banks et al., *supra* note 38.

intravenously crossed into the brain, with different concentrations in different neuroanatomic structures[.]” Pet’rs’ Ex. 37 at 8 (citing Pet’rs’ Ex. 37, Tab M, ECF No. 93-9). He noted that the “kinetics [were] indicative of a transport mechanism across the [blood-brain barrier].” *Id.* Dr. Miller testified that such a system “is well documented now to exist” but acknowledged that “[w]e don’t know a whole lot about that system.” Tr. 113:25–114:2. Dr. Miller noted that the process of active transport does not distribute cytokines everywhere and it is “probably . . . somewhat selective so that different places in the brain have receptors and pumps for different cytokines.” Tr. 114:5–7. He noted that “the medulla is probably one of the places” where the process works. Tr. 114:3–4. Dr. Miller testified that the transport process is not dependent upon inflammation or elevated temperature. Tr. 114:8–10. He further noted that researchers believe “that the fever comes about only after cytokines have reached the hypothalamus.” Tr. 114:12–14.

Dr. McCusker explained that there is “tight coordination between the peripheral system and the brain system.” Tr. 195:4–7 (discussing Resp’t’s Ex. A, Tab 13<sup>88</sup>). She testified that the blood-brain barrier was once thought to be essentially impermeable, but it is now understood that it “is a very metabolically active site, which allows for [the] regulation of messaging from . . . outside of the CNS, the rest of the body, and the brain.” Tr. 193:19–194:4. However, Dr. McCusker emphasized that “this messaging is not willy-nilly[;] it’s also regulated and tightly controlled so that messages that are being passed from the periphery into the brain . . . actually follow[] a path to signal a specific event.” Tr. 194:5–10. She emphasized that cytokines are not “flooding into the brain and going everywhere;” instead, there are “specific pathways that are taken to signal in the CNS.” Tr. 194:13–16. Dr. McCusker noted that with every known mechanism by which cytokines can cross the blood-brain barrier, they do not “just flood into the brain.” Tr. 327:19–20. She testified that the cytokines may require active transport, whereby specific receptors would bind with certain cytokines at the blood-brain barrier. Tr. 328:6–11.

Dr. Miller clarified that he does not believe that the brain “gets flooded with cytokines under most circumstances,” including “in the circumstances that lead to SIDS.” Tr. 367:23–25. Instead, Dr. Miller explained that, in his opinion, “very small quantities can tip a balance” in the brain of a vulnerable infant. Tr. 368:11–17. He noted that a vulnerable infant’s 5-HT system is “already in peril” and therefore, amounts that may not otherwise cause a problem in the brain “can be enough to tip the balance over and lead to catastrophe.” Tr. 368:15–17.

Dr. Miller testified that there are “just no data” on how long IL-1 $\beta$  can stay active in the brain once transported across the blood-brain barrier. Tr. 370:18–21. He explained that “it’s an experiment that would be impossible to do in humans, for ethical reasons,” and that “it would be very difficult to do it in most animal models, because we don’t have a really good animal model where we can predict there’s going to be SIDS.” Tr. 371:8–14.

## **2. Evidence Regarding Whether Cytokines Can Have an Effect on the Medullary Serotonin System**

Dr. Miller explained that studies look at the effects of one or two cytokines at a time “because the data will be too confusing” if researchers attempt to “look at a soup of multiple cytokines.” Tr. 68:1–4. Dr. Miller testified that the published literature primarily considers IL-1,

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<sup>88</sup> Ron-Harel et al., *supra* note 82.

IL-6, and TNF. Tr. 68:4–6. He described experiments which have shown that certain cytokines, especially IL-1 $\beta$  and IL-6, “have depressive effects on the serotonin system in the medulla and can suppress whatever arousal mechanisms might remain in an infant with a maldeveloped or damaged medulla.” Pet’rs’ Ex. 12 at 4 (citing Pet’rs’ Exs. 22,<sup>89</sup> 23,<sup>90</sup> 24<sup>91</sup>); *see also* Tr. 72:10–16. As noted previously, serotonin neurons “mediate arousal from apnea.” Tr. 76:22. Therefore, Dr. Miller explained, when IL-1 $\beta$  is introduced, “recovery from apnea, sensing elevated levels of carbon dioxide in the blood, [and] producing arousal and gasping respirations are all suppressed” when compared with situations where the cytokine is not present. Tr. 73:8–14.

Dr. Miller noted that there are not very good animal models for SIDS in general. Tr. 103:16–18. He emphasized that the piglets in the Stoltenberg and Frøen studies, discussed below, were “normal,” whereas “[a]n animal model of SIDS would hopefully be a spontaneous model in which you have some strain of animals which predictably die at a certain age of what appears to be from a full pathologic examination at death to be SIDS.”<sup>92</sup> Tr. 103:19–104:10. He explained that the studies involving piglets looked “at the question of recovery from apnea” and “whether those cytokines, [IL-1 $\beta$ ] in particular, suppress the serotonin system.” Tr. 103:23–104:1. Although he opined that the studies “can have applicability to understanding what may be happening in SIDS,” he explained that they are “not . . . animal model[s] of SIDS, per se.” Tr. 104:4

Dr. McCusker concluded that the three animal studies and three post mortem studies cited by Petitioners’ expert “do not show evidence for the role of cytokines, either those constitutively expressed in the brain or those found in the peripheral immune system, in suppressing the arousal mechanisms of the ‘maldeveloped or damaged medulla’ . . . as claimed by Petitioners’ [e]xpert.” Resp’t’s Ex. A at 8. Dr. McCusker repeatedly emphasized that “the dose required to induce [apnea] in the newborn piglets was supra-therapeutic.” Resp’t’s Ex. E at 7. Dr. McCusker noted that the Stoltenberg et al. study and “the follow up work” by Frøen et al. showed “the effect of suprathreshold doses of IL[-]1 $\beta$  was detectable only in the *neonatal animals and did not occur in animals older than 10–15 days*.” Resp’t’s Ex. A at 7 (citing Pet’rs’ Exs. 22,<sup>93</sup> 23<sup>94</sup>) (emphasis in original). She also emphasized that the authors of the Frøen et al. study “noted that similar experiments using IL[-]6 had no effect on respiration.” *Id.*

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<sup>89</sup> Stoltenberg et al., *supra* note 39.

<sup>90</sup> Frøen et al., *supra* note 40.

<sup>91</sup> Brambilla et al., *supra* note 41.

<sup>92</sup> Dr. Miller noted that “[p]igs mature far faster than human infants and so do their brains.” Pet’rs’ 37 at 8. Therefore, “[n]eonatal piglets may represent a reasonable model for human infants at the ages at which SIDS is observed[.]” *Id.* He emphasized that “the brains of piglets aged 13–14 days are explicitly comparable to those of human infants aged 2–4 months.” *Id.* Dr. Miller conceded that, “like all animal models[,] there are aspects of the model system that more or less closely mimic the human disease[,] whereas other aspects [d]o not.” *Id.* However, the purpose of using very young piglets in the Frøen and Stoltenberg studies “was to find an animal model [of] something like a 2[-]month[-]old human[.]” *Id.* Dr. McCusker testified that “you could argue back and forth” about whether a piglet aged six to ten days is comparable to a two-to-four-month old infant. Tr. 326:2–6.

<sup>93</sup> Stoltenberg et al., *supra* note 39.

<sup>94</sup> Frøen et al., *supra* note 40.

Dr. McCusker wrote in her report that the “literature demonstrates that cytokines IL[-]1 $\beta$ , IL[-]6 and TNF[-] $\alpha$  play important roles in the architecture of sleep and arousal and are constitutively expressed in the brain.” *Id.* at 8. She wrote that “[s]ystemic cytokine release can induce fever and changes in sleep patterns.” *Id.* However, Dr. McCusker opined that the changes caused by cytokines “affect the development of REM sleep resulting in greater frequency of arousal found in NREM sleep.” *Id.* Therefore, Dr. McCusker argued that “increases in IL[-]1 $\beta$  would affect sleep architecture to decrease deep REM sleep and increase NREM associated with more frequent and easy arousal.” *Id.* In other words, she opined that the “hypothesis that systemic cytokine[] release reduces the capacity for arousal in at risk infants[,] leading to SIDS[,]” is unsupported. *Id.*

Dr. McCusker argued that if Dr. Miller’s theory that “vaccine[s] induced significant increases in the cytokine IL[-]1 $\beta$ ” in J.J.’s brain were true, “the resulting effect would most likely have been increased arousal.” *Id.* at 5. She wrote that although “low levels [of IL-1 $\beta$ ] may promote NREM sleep, high levels have been shown to promote arousal.” *Id.* (citing Pet’rs’ Ex. 24<sup>95</sup>). She also wrote that “[e]vidence suggests that the central functions of the cytokines IL[-]1 $\beta$ , IL[-]6 and TNF[-] $\alpha$  at times of infection are to promote fever and to affect the sleep architecture by increasing NREM versus REM sleep resulting in more disturbed sleep with more frequent arousal[,] while permitting the maintenance of increased body temperature.” Resp’t’s Ex. A at 5 (citing Resp’t’s Ex. A, Tabs 19,<sup>96</sup> 20,<sup>97</sup> 21<sup>98</sup>). Dr. McCusker wrote that “cytokine activation would be protective . . . rather than pathologically linked to failure to arouse.” Resp’t’s Ex. A at 5 (citing Resp’t’s Ex. A, Tab 17,<sup>99</sup> ECF No. 39-7). She wrote that this is because “immune stimulation results in increased in TPH2, which increases 5-HT and augment[s] the protective arousal mechanism.” *Id.*

**i. Stoltenberg et al. – Pet’rs’ Ex. 22<sup>100</sup>**

Dr. Miller testified that in the Stoltenberg et al. study, apnea was induced in the piglets and the study looked at how quickly they recovered. Tr. 64:6–8. Dr. Miller testified that some of the piglets were injected with IL-1 $\beta$ , either in the blood or into the cerebrospinal fluid, and those piglets’ recovery times were compared with piglets which were “not manipulated with any other drugs or any other chemicals” other than those inducing the apnea. Tr. 64:8–15. Dr. Miller testified that the IL-1 $\beta$  “produce[d] delayed recovery and impaired recovery from apnea.” Tr. 64:13–15.

Dr. McCusker emphasized that when this study was conducted in 1994, the authors “thought that the blood-brain barrier was impermeable and that any presence of cytokines in the brain must mean that there was an infection or an insult to the brain.” Tr. 215:10–14. Therefore,

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<sup>95</sup> Brambilla et al., *supra* note 41.

<sup>96</sup> Clinton et al., *supra* note 45.

<sup>97</sup> Gamaldo et al., *supra* note 46.

<sup>98</sup> Rohleder et al., *supra* note 47.

<sup>99</sup> Guo-Lin Chen & Gregory M. Miller, *Advances in Tryptophan Hydroxylase-2 Gene Expression Regulation: New Insights into Serotonin-stress Interaction and Clinical Implications*, 159B AM. J. MED. GENETICS NEUROPSYCHIATRY GENETICS 152 (2012).

<sup>100</sup> Stoltenberg et al., *supra* note 39.

she opined that the authors “were looking for why [they were] finding these cytokines in the CNS.” Tr. 215:17–18.

Dr. McCusker acknowledged that the piglets’ apnea events were prolonged but noted that “they really needed to use high doses” of IL-1 $\beta$  to find results, also referring to them as “massive doses.” Tr. 215:21–216:16. She testified that “doses are important with cytokines.” Tr. 216:6–7. Dr. McCusker testified that even in a cytokine storm, “which is the worst release of cytokines that we can think of,” the levels of cytokines are lower than what was administered to the piglets in the study. Tr. 216:8–11. Therefore, she opined, the levels are “way over what you would see in a vaccine response[] and/or any kind of normal routine infection response.” Tr. 216:13–15.

Additionally, Dr. McCusker opined that the authors “had to use really young piglets, because they found that if the piglets were older than ten days, they no longer could induce this [apnea] event.” Tr. 216:17–20. Dr. McCusker opined that a 10-day-old piglet, depending on which literature one looks at, approximately equates to an infant who is “just under two months” old. Tr. 217:7–11. Therefore, she criticized the study because it was not “even dealing with piglets in the risk time that you would see for sudden infant death.” Tr. 217:18–20.

Dr. McCusker opined that “if we did the exact same thing with insulin,” or if one injected “1,000 times the dose” of insulin that normally circulates, “you would kill the animal.” Tr. 216:23–217:1. Therefore, Dr. McCusker opined that “to say it’s physiologically relevant is problematic.” Tr. 217:2–3. She testified that the authors “actually say that in their article. It’s not like they’re hiding anything.” Tr. 217:3–4.

**ii. Frøen et al. – Pet’rs’ Ex. 23<sup>101</sup>**

Dr. Miller also testified about the Frøen et al. study. Tr. 64:16–65:4. He explained that the purpose of that study was to look at the effects of nicotine and IL-1 $\beta$  on the piglets’ recovery from apnea episodes. Tr. 64:20–25. Dr. Miller testified that the study’s authors found that IL-1 $\beta$  “inhibited recovery” and that if nicotine and IL-1 $\beta$  were both present, “it was even worse.” Tr. 65:1–4.

Dr. McCusker testified that the authors of the Frøen et al. study “managed to dial back the dose [of IL-1 $\beta$ ] a little bit,” when compared with the Stoltenberg et al. study. Tr. 218:5–6. She testified that although the dose was “cut . . . in half . . . it’s still over 1,000 times more [than] what you see in the blood.” Tr. 218:6–7. Therefore, she opined that “they still needed a ton of cytokine in order to see any effect.” Tr. 218:15–16. Additionally, Dr. McCusker noted that the authors “tried to do the same thing with IL-6,” because “IL-6 is the [cytokine] that[ is] really found in the brain of [infants who die from] SIDS,” but that the authors could not “find any effect of giving high dose of IL-6 on this model.” Tr. 218:14–23.

**iii. Brambilla et al. – Pet’rs’ Ex. 24<sup>102</sup>**

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<sup>101</sup> Frøen et al., *supra* note 40.

<sup>102</sup> Brambilla et al., *supra* note 41.

Dr. Miller explained that the authors of the Brambilla et al. study used “brain slices,” or “very thin slices of living tissue,” from rat brains to study the effect of IL-1 $\beta$  on the serotonin system. Tr. 74:8–15. The tissue was kept in a bath to keep it alive, and the activity of the cells was monitored. Tr. 74:11–14. Dr. Miller testified that the authors “took the relevant areas of serotonergic neurons in the brain stem of these rats” and added IL-1 $\beta$  to the bath solution. Tr. 74:16–19. When that happened, Dr. Miller testified, the activity of the serotonin system was suppressed, whereas the activity of gamma-aminobutyric acid (“GABA”),<sup>103</sup> “which is the inhibitory system that kind of interacts with the serotonin system,” increased. Tr. 74:20–24. Therefore, Dr. Miller testified, “the net effect was even more suppression.” Tr. 74:24–25. He noted that although arousal cannot be observed in brain slices, “these are the neurons that mediate arousal,” so the inference is that in a whole living animal “there would have been less arousal.” Tr. 75:2–6.

Dr. McCusker testified that “the relative significance [of the findings in the Brambilla et al. study] is not clear, because of the massive amounts of IL-1 $\beta$  that was required” to have an effect on the studied brains. Tr. 226:23–227:1. She noted that the article admits that “[t]he precise effects of IL-1 $\beta$  on vigilant states are complex[] and depend on dose and timing administration.” Tr. 227:2–7; *see* Pet’rs’ Ex. 24 at 6. Dr. McCusker testified that IL-1 $\beta$ , when injected intracerebroventricularly,<sup>104</sup> “increases NREM sleep across an effective dose range of 2.5 to 10 nanograms,” which is “significantly” above the picogram level. Tr. 227:7–13. She also testified that “doses greater than 10 nanograms, when injected intracerebroventricularly, disrupt NREM sleep and promote arousal.” Tr. 227:11–13.

Dr. McCusker testified that the Brambilla study used “supratherapeutic doses” and analogized that “[i]nsulin in these level differences would kill you.” Tr. 227:14–17. She emphasized that “a constant dose of 25ng/ml of IL[-]1 $\beta$  was required to demonstrate any effects on the neurons[]” and argued that “there is no evidence that extremely high levels of IL[-]1 $\beta$  needed to suppress the *in vitro* GABAnergic responses are achieved via peripheral vaccination.” Resp’t’s Ex. A at 8. In contrast, Dr. McCusker wrote that “only picogram amounts of IL[-]6 w[ere] detectable and IL[-]1 $\beta$  was undetectable in the peripheral circulation[]” for children after vaccination in the Kashiwagi et al. study. *Id.*

Although Dr. Miller acknowledged that the Brambilla et al. study used 25,000 picograms of IL-1 $\beta$  per millimeter, he noted that the amount was “potentially . . . diluted by a lot” due to the culture system used to bathe the brain slices in that study, “which is a continuously running bath.” Tr. 344:1–6. He noted that the amounts measured in the blood of vaccinated subjects studied in the Kashigawa et al. study were “on the same order of magnitude,” and “certainly not thousands of times different,” despite the lack of IL-1 $\beta$  data in those subjects. Tr. 346:19–347:1.

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<sup>103</sup> Serotonergic dorsal raphe nucleus neurons are inhibited by GABA. Pet’rs’ Ex. 24 at 1. “GABA plays a crucial role in shaping the state-dependent firing and neurotransmitter release of serotonergic neurons, which are highly active during wakefulness, reduce their activity during NREM sleep and are almost silent during REM sleep.” *Id.* at 1–2.

<sup>104</sup> Intracerebroventricular is within the ventricles of the brain. *Dorlands* at 953.

**iv. Kadhim et al. – Pet’rs’ Exs. 25<sup>105</sup> and 27<sup>106</sup> and Resp’t’s Ex. H<sup>107</sup>**

Dr. Miller discussed a 2003 study authored by Kadhim et al., which looked at cytokines in the brain of infants who died from SIDS. Tr. 58:12–15 (discussing Kadhim et al., *supra* note 79). He testified that IL-1 $\beta$  “was found in the arcuate nuclei, [which is] the same nuclei that can sometimes be deficient in SIDS babies, and in the . . . dorsal vagal nuclei.” Tr. 58:24–59:1. Dr. Miller testified that this “elevated immune activity” was not found in the brains of infants who died from other causes. Tr. 59:11–14.

Dr. McCusker emphasized that in Table 1 of that study, “cytokine staining was elevated in the . . . brains of children who had SIDS and had evidence of infection, but also . . . in children who had SIDS without evidence of infection.” Tr. 213:4–8. Based on that data, Dr. McCusker opined that IL-1 $\beta$  “is unregulated in the brains of SIDS [infants], regardless of a history of infection.” Tr. 213:9–11. She testified that “if, as Dr. Miller is suggesting . . . with infection and/or vaccination, the increase of cytokines isn’t is [sic] coming from . . . the signaling in the peripheral immune system, you would expect to see a difference based on whether or not [the infant] . . . had evidence of infection.” Tr. 213:13–18. Dr. McCusker emphasized that there is no difference between the two in the chart. Tr. 213:18–19. Therefore, in her opinion, the data shows that “cytokines [ and] neurokines, are constitutively expressed in brains.” Tr. 213: 20–22. Furthermore, she opined that the cytokines are “a response marker,” increased in response to the stressor which leads to the terminal event, “as opposed to a causative marker.” Tr. 213:24–214:3. Therefore, Dr. McCusker opined that the Kadhim et al. study supports the IL-1 $\beta$  increase, “but it doesn’t support that a peripheral immune response can induce that increase.” Tr. 214:13–15. Dr. McCusker testified that IL-1 $\beta$  may be up-regulated in the brain of infants who died from SIDS because “there is disordered sleep and respiration, and the body is trying to reorder it.” Tr. 230:9–13. She testified that such a hypothesis is “as reasonable . . . as anything, based on this series of articles.” Tr. 230:13–14.

Dr. McCusker wrote that the 2010 Kadhim et al. article compared IL-2 levels in the brains of infants who died from SIDS to the brains of infants who died of other causes, and “showed no difference in expression in” IL-2. Resp’t’s Ex. A at 8 (citing Kadhim et al., *supra* note 71). She wrote that the authors of that study “hypothesize that IL[-]2, like the cytokines IL[-]1 $\beta$ , TNF[-] $\alpha$  and IL[-]6, may be expressed in normally functioning brains of infants.” *Id.* Dr. McCusker testified that IL-2 was increased in the brain of infants who died from SIDS but criticized that the Kadhim et al. article does not “talk about what the cytokine is doing there, or whether it’s implicated [in SIDS]. . . [or] . . . try and draw . . . a line that says it’s doing anything damaging in the CNS following vaccin[ation], is just not there.” Tr. 242:5–12.

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<sup>105</sup> Kadhim et al., *supra* note 79.

<sup>106</sup> Kadhim et al., *supra* note 81.

<sup>107</sup> Hazim Kadhim et al., *Selective Expression of a Neuromodulatory Cytokine (IL-2) in Specific Brainstem Neurovegetative Centers: A Possible Final Common Neuro-molecular Pathway in Dying Patients*, 78 MEDICAL HYPOTHESES 793 (2012).

During her testimony, Dr. McCusker also discussed a third article authored by Kadhim. Tr. 236:2–8.<sup>108</sup> She explained that this 2012 Kadhim study “actually looked at the brains of adults who died and found the exact same signaling that they found in the SIDS brains,” which suggested that the signaling is “probably related to sort of what’s happening in a terminal brain event as opposed to being specific for SIDS.” Tr. 236:3–8.

**v. Rognum et al. – Pet’rs’ Ex. 26<sup>109</sup>**

Dr. Miller discussed the Rognum et al. study, entered as Petitioners’ Exhibit 26. Tr. 59:15–16. He explained that the authors “were testing the hypothesis that the IL-6 receptors and the gp130 expression would be altered in the medulla in SIDS patients.” Tr. 60:4–7. He testified that the authors found increased amounts of IL-6 receptors in the arcuate nucleus in infants who died from SIDS when compared with those infants in the control group. Tr. 60:8–12. The authors concluded that “aberrant interactions in SIDS infants between IL-6 and the arcuate nucleus may contribute to impaired responses to hypercapnia generated by infection combined with rebreathing.” Pet’rs’ Ex. 26 at 9. Dr. Miller concluded that “it means that in SIDS babies who have defects in those nuclei, there is a change in the expression of the cytokine, or in the binding of this cytokine, and its receptors, compared to . . . normal infants who have died of something else.” Tr. 61:22–62:3.

Dr. McCusker also discussed the Rognum et al. study. Dr. McCusker wrote that the authors of that study “postulate from [their] data that the role of infection in SIDS is likely due to mild upper *respiratory tract infections influencing respiration resulting in increased CO2 levels in infants rather than the influence of the infection on brain cytokine levels.*” Resp’t’s Ex. A at 8 (emphasis in original).<sup>110</sup> Dr. McCusker testified that the Rognum et al. study was done because there was conflicting literature on whether IL-6 was associated with the brain of infants who died from SIDS. Tr. 231:5–12. She noted that “part of the theory for the presence of the IL-6 was this idea that mild infection[s] release[] cytokines, and so maybe that’s why there’s more IL-6 in the brains of SIDS patients with infection.” Tr. 231:13–17.

Dr. McCusker testified that the authors “compared children whose final diagnosis was SIDS to a control group, a couple of control groups, and within the SIDS diagnosis, they looked at children who ha[d] evidence of mild infection versus those that did not.” Tr. 231:19–23. She testified that the authors found the presence of infection made “no difference in the IL-6 levels” in the brain of infants who died of SIDS, “suggesting that IL-6 in those children’s brains was not there specifically because of the infection.” Tr. 231:24–232:3. More importantly, Dr. McCusker explained that gp130 is a “key co-factor, a key protein that needs to be there . . . functioning, in

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<sup>108</sup> Petitioners objected to the introduction of this article, which Dr. McCusker stated that she did not rely upon while writing her reports but found “later on” while “scanning the literature for new articles” in an effort to keep up to date for future testimony in Vaccine Program cases. Tr. 237:5–19. Dr. Miller acknowledged that the article “came up in another case in which [he] testified in December,” so he is “loosely aware” of it but had not “had a chance to review it in detail.” Tr. 238:6–8. Dr. Miller opined that the article was “sort of sprung on us in December.” Tr. 238:9.

<sup>109</sup> Rognum et al., *supra* note 44.

<sup>110</sup> But the abstract of this study says “[m]ild infection may trigger sudden death in the vulnerable infant by cytokine interactions with a compromised medullary serotonergic (5HT) system[.]” Pet’rs’ Ex. 26 at 1.

order for that signal to go through.” Tr. 232:17–19. The authors noted in the study that “[i]t is essential that gp130 be present on the cell membrane for IL-6 to elicit neuronal responses.” Pet’rs’ Ex. 26 at 8. Dr. McCusker put this relationship in context and explained that “there was a disconnect between the IL-6 receptor expression and the gp130 expression” in the brain of infants who died from SIDS, “such that the signaling was going to be dysregulated, meaning that if the IL-6 bound to the IL-6 receptor, there was no gp130 to transmit the signal on.” Tr. 232:20–25. Therefore, if infection and vaccination “can flood the brain with IL-6,” then the brain cells would be “unable to respond to it [and] it would be as if it didn’t exist there, because it can’t signal through IL-6.” Tr. 233:1–6. She explained that “the IL-6 might be there because the brain is producing it in response to the stressor that it’s feeling as it’s dying, and the receptors that are supposed to respond to it can’t[,] so it keeps producing more because that’s the right response to IL-6, but the receptors can’t hear it.” Tr. 233:1–617–25.

Although Dr. McCusker acknowledged that the “hypothesis of the paper” was that SIDS may be triggered by mild infections due to cytokine interaction with a compromised medullary serotonergic system, she testified that she disagreed with such a conclusion. Tr. 267:10–18. Dr. McCusker opined that the conclusion of the paper is that IL-6 “may be related to the response to the infection or the stressor that the baby is undergoing, and not be related to actually a mechanistic causality association.” Tr. 268:7–10. Dr. McCusker testified that the authors do not “think that their thesis at the beginning of [the paper] is supported by the data that they showed.” Tr. 270:21–23.

### **3. Evidence Regarding Whether Cytokines Are Produced in Response to Vaccination**

Dr. Miller testified that cytokines “can start to appear pretty rapidly” after vaccination. Tr. 83:18. More specifically, he testified that they can appear within “just a few hours.” Tr. 83:18–19. He noted that the literature has generally considered cytokine levels 24 or more hours after vaccination, but that “certainly 12 hours is enough for them to be detectable.” Tr. 83:19–23.

Dr. McCusker wrote that when an immune response is initiated, “cytokines are often released in the local environment and are part of the initial cascade of inflammation at the site of infection or trauma.” Resp’t’s Ex. A at 3–4. She opined that “[m]ost cytokine events occur locally and do not generate significant systemic signaling.” *Id.* at 3. Instead, she opined that they “are usually transient and tightly regulated.” *Id.* at 4 (citing Resp’t’s Ex. A, Tab 10<sup>111</sup>). However, she wrote that “[a]n example of systemic effects of cytokines is the induction of fever[.]” *Id.* at 3.

Dr. McCusker wrote that “[v]accination results in the production and release of multiple cytokines in a tightly regulated manner.” Resp’t’s Ex. E at 6. Furthermore, “cytokines may have different effects depending upon the location of their release, [and therefore] the concentration and duration of activity . . . are important considerations.” *Id.* at 7.

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<sup>111</sup> Lucile Capuron & Andrew H. Miller, *Immune System to Brain Signaling: Neuropsychopharmacological Implications*, 130 PHARMACOLOGY & THERAPEUTICS 226 (2011).

Dr. McCusker wrote about two studies of post-vaccination cytokine levels. Resp't's Ex. A at 4 (citing Resp't's Ex. A, Tabs 11,<sup>112</sup> 12,<sup>113</sup> ECF Nos. 39-1, 39-2). She opined that the studies “suggest that cytokines are produced and released by the peripheral immune system during vaccination[.]” but that “there is no evidence to suggest that the levels are sufficient to influence the brain serotonergic pathways[.]” *Id.*

Dr. McCusker acknowledged that one of the studies showed serum IL-6 levels were similar in infants with influenza infection and those evaluated within 48 hours after vaccination. *Id.* at 6 (citing Resp't's Ex. A, Tab 12). However, she noted that the “serum cytokine levels were independent of signs of CNS activity such as fever.” *Id.* Therefore, Dr. McCusker argued that the study's “findings show that UR[Is] and vaccination do not represent pathophysiologically equivalent events in children with SIDS.” *Id.*

In support of his theory that vaccinations cause an infection-like cytokine response in the body, Dr. Miller also cited the study authored by Kashiwagi et al. Pet'rs' Ex. 37, Tab K,<sup>114</sup> ECF No. 93-7. The authors studied *in-vitro* peripheral blood mononuclear cells (“PBMCs”) after stimulation with vaccine components, as well as serum samples obtained from vaccine recipients. *Id.* The study revealed measurable levels of the cytokines IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and G-CSF in the PBMCs. *Id.* at 3, Figure 1. With the exception of IL-1 $\beta$ , the authors also found detectable amounts of those same cytokines in the serum of vaccinated subjects, at similar levels regardless of whether a vaccine recipient developed a fever after vaccination. *Id.* at 6, Table 2. When compared with the levels of subjects who did not receive vaccines, the authors found higher levels of IL-6, IL-10, IL-12, G-CSF, IFN- $\gamma$ , and TNF- $\alpha$  in all vaccine recipients, whether they were febrile or non-febrile. *Id.* at 5. The cytokine levels of vaccine recipients were also compared with patients with acute infections, and the authors found similar cytokine levels in the two groups. *Id.* at 5–6.

Dr. Miller emphasized in his testimony that “there were very few if any differences between people who were sick with the flu and people who had been vaccinated,” in terms of cytokines present in the blood. Tr. 71:12–16. He noted that the cytokines produced by the *in vitro* cells were also similar, with the exception that “significant quantities” of IL-1 $\beta$  could be detected in the cultures, whereas “only trivial quantities” of that cytokine could be detected in the blood of vaccinated or ill patients. Tr. 71:17–21. However, Dr. Miller testified that the authors “think[] that they just missed the peak of [IL-1 $\beta$ ] production because it's earlier than the time they sampled the blood.” Tr. 71:22–25; *see also* Tr. 66:12–18.

Dr. McCusker explained that the authors of the Kashiwagi et al. study “[o]f course” found that cytokines were up-regulated in response to vaccination and noted that “[t]hat's what's supposed to happen.” Tr. 221:8–10. However, she explained that “we expect them to act locally, we do not expect them to go systemic.” Tr. 221:15–16. She opined that the cytokine response seen in the *in vitro* PBMCs “would be the equivalent of what is happening, and even that's not true, but of what is happening in the lymph node next to the site of vaccination, because it's a

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<sup>112</sup> Hingorani et al., *supra* note 86.

<sup>113</sup> Yasuyo Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-pertussis-tetanus (DPT), Haemophilus Influenzae Type b (Hib), and 7-valent Pneumococcal (PCV7) Vaccines*, 10 HUM. VACCINES & IMMUNOTHERAPEUTICS 677 (2014).

<sup>114</sup> *Id.*

contained environment, and you're having the cells being stimulated by the presence of the vaccine components." Tr. 219:23–220:2. She testified that "if you think about the lymph node as a pond, you could see those levels" which are reflected in the study. Tr. 220:10–11. However, she explained that "when you talk about those levels in the peripheral circulation, it's like you open the dam, and now those cytokines fall out into the rushing stream of the systemic circulation." Tr. 220:12–14. Therefore, the concentration measured in the lymph is "diluted by the circulating blood volume," and the "levels are going to go way down." Tr. 220:15–18. Additionally, Dr. McCusker criticized the study because cytokines "operate over very short distances[] and they have a very short half[-]life . . . most of the conversation is going to be in the cells next to them[.]" Tr. 220:21–24. Therefore, she opined that "what happens in the dish" is not equivalent to "what's going to get up to the brain." Tr. 221:5–6. Dr. McCusker testified that "you're not going to get this massive amount of cytokine running up to the brain." Tr. 221:17–18.

Based on her analysis of the cytokine response in the PBMCs, Dr. McCusker opined that it was "[n]ot a surprise" that there were "not too much [sic] cytokines in the peripheral circulation." Tr. 221:14–16. She noted that the authors measured serum cytokine levels in picograms, which she testified are "tiny." Tr. 225:16–17. Additionally, Dr. McCusker specifically noted that IL-1 $\beta$  was "undetectable" in the patients' serum. Tr. 224:18–20. She agreed with Dr. Miller that "the obvious limitation" in the Kashiwagi et al. study "is the fact that the cytokine levels were measured . . . between 24 and 48 hours after the vaccine," which is beyond the time frame relevant to this case. Tr. 225:20–25. However, she testified that "even if you look at the cytokine levels that [the authors] report . . . in the dish, you're still looking at picogram amounts." Tr. 226:1–3. Therefore, she testified that the amounts are "still well below what was needed in the Stoltenberg and Frøen articles" to prolong apneas. Tr. 226:3–5.

Dr. Miller and Dr. McCusker both testified about the significance of the unit of measurement used to describe the cytokine levels described in these studies.<sup>115</sup> Dr. Miller testified that a picomole is "10 to the minus 12 moles." Tr. 357:6. A mole, he explained, is a quantity that is "6.02 times 10 to the 23rd power" molecules. Tr. 357:11–13. He explained that these are "really, really small quantities, not something that we are familiar with in every day life." Tr. 358:16–18. He emphasized that the amount could not be measured outside of a laboratory. Tr. 358:19–22.

After providing this context, Dr. Miller countered Dr. McCusker, stating "things that are in picogram quantities are hardly something you can characterize as massive." Tr. 346:18–20. Dr. Miller testified that in the *in vitro* experiments in the Kashigawa et al. study, the highest number of cytokines the authors found for IL-1 $\beta$  was 510 picograms per milliliter. Tr. 342:13–20. Dr. Miller then compared the amount produced in the Kashiwagi et al. study to the amount injected into piglets to study the effect of cytokines on apnea and autoresuscitation. He testified that in the Stoltenberg et al. study,<sup>116</sup> "[t]he intravenous injections used IL-1 $\beta$  at 20 picomoles" and "you have to do a conversion." Tr. 340:21–341:18. Dr. Miller then explained that the conversion is

<sup>115</sup> Dr. Miller testified that he relied on Graphpad for his calculations. Tr. 339:2–5.

<sup>116</sup> Stoltenberg et al., *supra* note 39.

done using “the molecular weight of IL-1 $\beta$  . . . [which] is 17.5 kilodaltons.”<sup>117</sup> Tr. 341:5–9. He stated that “[t]wenty picomoles is the same as 350 picograms.” Tr. 341:10–12. “And then for the intrathecal injections, they used half, so they used 10 picomoles, which is 175 picograms. Tr. 342:7–9. Dr. Miller concluded that 175 picograms per milliliter were introduced by intrathecal injection and 350 picograms per milliliter were introduced intravenously. Tr. 341:2–343:1. Regarding the Frøen et al. study,<sup>118</sup> he testified that “something like 367 picograms per injection” were used in the piglet studies. Tr. 343:21–22. Dr. Miller clarified his point that the cytokines described in the Kashiwagi, Stoltenberg, and Frøen studies were not similar in type, but in quantity. “I want to be careful . . . because what’s done in the Frøen and Stoltenberg [studies] is IL-1 $\beta$  and they didn’t detect IL-1 $\beta$  in the serotonin [in] any significant quantity in the living human beings from in their blood [in the Kashiwagi et al. study].” Tr. 347:6–10. He stated that he could not “say they’re exactly the same, but . . . it’s the same order of magnitude,” therefore, “this is a reasonable comparison.” Tr. 347:14–19. Dr. Miller noted that the doses administered in the animal studies “were administered to normal piglets.” Pet’rs’ Post-Hrg Reply Br., Appx. A, ECF No. 110-1.

Dr. McCusker strongly disagreed with Dr. Miller’s numbers and Respondent sought to clarify the calculations in post-hearing briefings. Resp’t’s Post-Hrg Resp. Br., ECF No. 106. Respondent provided worksheets that also used 17.5 kilodaltons as an appropriate multiplier. *Id.*; Resp’t’s Post-Hrg Resp. Br., Appx. A, B, ECF Nos. 106-1, 106-2. Respondent then argued that the conversion is 17.5 kilograms/mole or 17.5 nanograms/picomole. Resp’t’s Post-Hrg Resp. Br., Appx. A at 3. Ultimately, “20pmols = 350ng,” Resp’t’s Post-Hrg Resp. Br., Appx. A, B, i.e., “both Graphpad and manual calculations reflect that 20 picomoles of IL-1 $\beta$ , using a molecular weight of 17,500 daltons as the conversion method, is equivalent to 350 nanograms, which is 350,000 picograms.” Resp’t’s Post-Hrg Resp. Br. at 15–16 (emphasis in original).

#### IV. *Althen* Causation

##### A. Applicable Legal Standard

To receive compensation under the Vaccine Act, Petitioners must demonstrate either that: (1) J.J.’s death is a “Table Injury” and therefore resulted from the receipt of a covered vaccine or vaccines within the time frame prescribed by the Vaccine Injury Table set forth at § 14, as amended by 42 C.F.R. § 100.3; or (2) J.J.’s death is an “off-Table Injury,” one not listed on the Table, that resulted from his receipt of a covered vaccine. *See* § 11(c)(1)(C); *Moberly v. Sec’y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec’y of Health & Human Servs.*, 440 F.3d 1317, 1319–20 (Fed. Cir. 2006). Petitioners’ claim that J.J.’s vaccines caused his death does not fall within the Vaccine Table. Thus, it must be proven that his vaccines were the cause-in-fact of his death.

To establish causation-in-fact, Petitioners must demonstrate by a preponderance of the evidence that the vaccines were the cause of J.J.’s injury. § 13(a)(1)(A). Petitioners are required

<sup>117</sup> In post-hearing filings, Respondent provided conversion formulas for picomoles to picograms: 1. Determine how many moles are given in a problem; 2. Calculate the molecular mass of the substance; 3. Multiply step one by two. Resp’t’s Post-Hrg Br., Appx. A–B, ECF No. 106.

<sup>118</sup> Frøen et al., *supra* note 40.

to prove that the vaccine was “‘not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury.’” *Moberly*, 592 F.3d at 1321–22 (quoting *Shyface v. Sec’y of Health & Human Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)).

In *Althen v. Sec’y of Health & Human Servs.*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278 (Fed. Cir. 2005). The *Althen* test requires a petitioner to set forth: “(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.” *Id.* To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *See id.* (internal citations omitted).

Specifically, under the first prong of *Althen*, a petitioner must offer a scientific or medical theory that answers in the affirmative the question “can [the] vaccine(s) at issue cause the type of injury alleged?” *See Pafford v. Sec’y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at \*4 (Fed. Cl. Spec. Mstr. July 16, 2004). This may be accomplished in a number of ways. “Reliability and plausibility of . . . pathogenesis can be bolstered by providing evidence that at least a sufficient minority in the medical community has accepted the theory, so as to render it credible.” *Id.* Additionally, “epidemiological studies and an expert’s experience, while not dispositive, lend significant credence to the claim of plausibility.” *Id.* Medical literature published in respected medical journals is also persuasive. *Id.* “However, publication ‘does not necessarily correlate with reliability,’ because ‘in some instances well-grounded but innovative theories will not have been published.’” *Id.* (quoting *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 593–94 (1993) (emphasis in original)).

In addition to showing that the vaccine at issue can cause a particular injury, a petitioner must also, under *Althen*’s second prong, prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at \*4; *Althen*, 418 F.3d at 1278. A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; the petitioner “must explain *how* and *why* the injury occurred.” *Pafford*, 2004 WL 1717359, at \*4 (emphasis in original) (internal citations omitted).

Although a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. The special master cannot infer causation from temporal proximity alone. *See Thibaudeau v. Sec’y of Health & Human Servs.*, 24 Cl. Ct. 400, 403–04 (Fed. Cl. Oct. 23, 1991); *see also Grant v. Sec’y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992) (“[T]he inoculation is not the cause of every event that occurs within the ten[-]day period. . . . Without more, this proximate temporal relationship will not support a finding of causation.” (quoting *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983))).

A petitioner who demonstrates by a preponderance of the evidence that he or she suffered an injury caused by vaccination is entitled to compensation, unless Respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the

vaccination. *See Althen*, 418 F.3d at 1278; *Paluck v. Sec’y of Health & Human Servs.*, 786 F.3d 1373, 1386 (Fed. Cir. 2015) (citing *de Bazan v. Sec’y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008) (holding that it is not a petitioner’s burden “to rule out possible alternative causes” (internal citations omitted))); *Knudsen v. Sec’y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994).

## **B. Summary of the Parties’ Arguments under *Althen***

Petitioners requested post-hearing briefings to summarize their position and clarify additional evidence that was presented during the hearing for the first time. Petitioners’ theory can be summarized as an expansion of Dr. Kinney’s Triple Risk Theory. Dr. Miller identifies vaccines as an exogenous stressor analogous to infection and argues that like infection, vaccination causes an increase in the production of certain cytokines which can then travel to the brain. In an infant with a specific brainstem defect and other intrinsic factors commonly associated with SIDS, these vulnerabilities, coupled with the increased levels of cytokines following vaccination, can create a perfect storm that leads to SIDS due to a neurochemical failure to rouse during sleep. In this case, Dr. Miller contends that there is evidence of such a brain defect in J.J. and there is no evidence that he had an infection or any other condition that could more probably than not be the cause of his death. J.J. ultimately succumbed to SIDS because the increased levels of cytokines in his brain disrupted his 5-HT system and his arousal system failed. Dr. Miller further contends that this conclusion is supported by the short period of time that lapsed between J.J.’s vaccinations and death. Petitioners note that a “close examination of Dr. McCusker’s testimony demonstrates that is it [sic] marred by mischaracterization, and inconsistent statements that in some instances are contradicted by the articles she submitted . . . .” Pet’rs’ Post-Hrg Br. at 18, ECF No. 103. Indeed, there is some valid criticism of Dr. McCusker’s testimony, specifically as it relates to her over-reliance on specific literature to make a point.

Respondent argues that “Petitioners have not satisfied prong one of *Althen* because Dr. Miller’s theory that vaccines can cause SIDS is speculative and contradicted by the available medical literature.” Resp’t’s Post-Hrg Br. at 4. He criticizes Dr. Miller’s approach of “piecing together and relying on inferences and conclusions from many individual studies[]” to support his proposed theory. *Id.* at 6. Respondent argues that Petitioners’ theory of causation involves “a question of immunology, not neuropathology[]” and notes that Dr. Miller is not an immunologist. *Id.* at 6. In contrast, Respondent emphasizes that Dr. McCusker is a pediatric immunologist. *Id.*

Respondent contends that available literature does not provide support for Petitioners’ theory. Respondent argues that the extrinsic risk factors identified by Dr. Kinney et al. “are elements that contribute to a change in the mechanical ability of an infant to respire[]” and that Dr. Miller “improperly extends the Triple Risk Model by positing that cytokines provoked by

vaccination can be an exogenous stressor that leads to SIDS.”<sup>119</sup> *Id.* at 4–5. Respondent argues that “[t]here is no support in the extensive body of literature regarding SIDS that vaccines are an exogenous risk factor.” *Id.* at 5. He further argues that such a “theory appears to have been created solely for purposes of litigation[,]” noting that Dr. Kinney has not included vaccines among the exogenous stressors in her Triple Risk Model. *Id.* Respondent also notes that Dr. Miller “acknowledged that no peer-reviewed publication puts forth the hypothesis upon which he relies[]” and that he has insufficient data or information to publish a paper on his hypothesis. *Id.* at 5–6.

Respondent lastly argues that “there is no evidence that cytokine expression in the brain plays a role in SIDS.” *Id.* at 6. He argues that Petitioners’ literature which discusses the presence of cytokines in the brain of infants who have died from SIDS is only relevant to show that the cytokines are expressed in the brain and not that they have any effect on the brain. *Id.* Respondent states that “cytokine expression is evidence of the attempt to avoid damage, not the cause of damage.” *Id.* at 7. The problem for infants that succumb to SIDS “is not the presence of cytokines, but the inability to respond to them.” *Id.* Relatedly, Respondent argues that “it makes much more sense” that cytokines expressed in the brain are neuro-regulatory, rather than the theory that they were induced by vaccination in the thigh and traveled to the brain. *Id.*

### C. Prior Program Cases Involving SIDS

The question of whether vaccines can cause SIDS has been addressed in the Program previously. These cases contain similar facts and legal issues, and Drs. Miller and McCusker testified and presented similar arguments. Therefore, the undersigned will provide a brief overview of these cases below.

#### 1. *Lord v. Sec’y of Health & Human Servs.*

In *Lord*, petitioners’ experts (Drs. Miller and Oleske) both used a version of the Triple Risk Model as a framework for their causation theory, with the vaccines acting as an extrinsic risk factor. *Lord v. Sec’y of Health & Human Servs.*, No. 12-255V, 2016 WL 806818, at \*10–11 (Fed. Cl. Spec. Mstr. 2016). According to Dr. Miller, vaccination activates the immune system to produce peripheral cytokines in the same way a mild infection does, and these cytokines have the same effect on the nervous system as those produced by infection. *Id.* at 10. As the basis for this theory, Dr. Miller cited the article by Kashiwagi et al.<sup>120</sup> *Id.* This is the same argument that Dr. Miller proposes in the current case. Dr. McCusker was also Respondent’s expert in *Lord* as she is

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<sup>119</sup> Dr. Miller testified that “Dr. Kinney has never evaluated vaccinations one way or the other, and in discussions with her, she said she doesn’t want to go anywhere near the topic and she doesn’t testify in hearings such as this one.” Tr. 94:23–95:1. Dr. Folkert identified Dr. Kinney as her mentor and challenged this assertion. She testified that “[Dr. Kinney] has devoted her life to try and understand why babies die of SIDS.” Tr. 136:2–3. She continued, “if someone were to show that vaccines were responsible . . . she would be the first person to go out into the world and proclaim that we now have figured out the cause of SIDS.” Tr. 136:3–7. Dr. Folkert found it “ridiculous” that Dr. Kinney “is afraid of standing in front of judges” and noted that Dr. Kinney has “testified before Congress about SIDS.” Tr. 136:8–12. Given the contradictory statements of the experts, the undersigned will assign no personal motivations to the scope of Dr. Kinney’s work.

<sup>120</sup> Kashiwagi et al., *supra* note 113.

here. *Id.* at \*11–12. In addition to her argument that vaccines do not effect a mechanical change on the body and therefore do not qualify as extrinsic stressors under the Triple Risk Model, Dr. McCusker also argued that cytokine production in response to vaccination is localized and does not generate systemic signaling. *Id.* at \*12–13. Furthermore, she noted that at times of infection, cytokines promote fever and create a more disturbed sleep, which is counter to Dr. Miller’s argument that cytokines prevent arousal. *Id.* at \*13.

The chief special master agreed with Dr. McCusker and found that petitioners were unable to prove by a preponderance of the evidence that extrinsic risk factors can be neurochemical, nor that URIs are akin to vaccinations. *Id.* at \*15. The facts in *Lord* presented additional problems for petitioners because the chief special master found that the child had specific external stressors that could have played a role in his death, namely gastroesophageal reflux and prone sleeping, the position in which his grandmother found him. *Id.* at \*20.

## **2. *Copenhaver v. Sec’y of Health & Human Servs.***

Petitioners’ arguments in *Copenhaver* build upon the Triple Risk Model, and the mechanism described by Dr. Miller in that case is also very similar to his theory here. They argued that (1) the vaccinations induced the production of cytokines just as infections induce cytokine production; (2) the cytokines crossed the blood-brain barrier to reach the part of the brain responsible for auto-resuscitation; (3) for some unknown reason, Minor A stopped breathing; and (4) Minor A’s brain could not initiate the normal auto-resuscitation response because the cytokines impaired the brain’s functioning. *Copenhaver*, 2016 WL 3456436, at \*6. The facts in the *Copenhaver* case are distinguishable because the child suffered from symptoms indicative of an infection, including a low-grade fever and vomiting several hours after his vaccinations. *Id.* at \*4. Additionally, the child in that case did not succumb to SIDS until two days after vaccination. *See id.* Finally, and most importantly for the causation theory itself, the child in *Copenhaver* had a hippocampus malformation, which could be a potential case for seizures, and swelling in the cerebellum. *Id.* at \*5. He did not, however, have an arcuate nuclei defect. *Id.* In the present case, Dr. Miller relies on evidence that J.J. suffered from this specific type of defect to identify a vulnerability that J.J. had to make him more susceptible to SIDS.

The special master considered Dr. Miller’s theory but did not find his theory persuasive. Dr. Miller is a neuropathologist, however, his knowledge of cytokine production and effect on the body is not based on direct research or clinical work. *Id.* at \*10. He is not an immunologist. *Id.* Comparatively, Dr. McCusker, a pediatric immunologist, has conducted research focused on cytokine production. *Id.* at \*10–11. Her testimony was more persuasive to the special master in this case because of her understanding of cytokines and ability to explain how Dr. Miller’s theory is inconsistent with the way cytokines affect the body. *Id.* at 11.

## **3. *Jewell v. Sec’y of Health & Human Servs.***

The facts in the *Jewell* case are similar to those in the present case, in that the child did not show any signs of infection or illness following vaccination but was described by the mother as fussy prior to bedtime. *Jewell*, 2016 WL 5404165, at \*2. The timeline is also similar in that the children succumbed to SIDS approximately 12 hours after vaccination. *See id.* at \*1–2. Drs.

Miller and McCusker were again two of the experts that testified in *Jewell*. Dr. Miller's argument in that case was similar to the one he made in *Copenhaver* and *Lord*; however, in *Jewell* he believed that the child had a defective arcuate nucleus. *Id.* at \*5. Dr. Miller argued that in children with this defect, which is present in 70 percent of SIDS cases, vaccines and the cytokines that they produce may serve as an exogenous stressor by depressing the activity of 5-HT neurons in an already defective system. *Id.* at \*5–6.

Dr. McCusker responded that cytokines could not suppress the respiratory response in a brain with a defective 5-HT system because, by the nature of the defect, the system is incapable of responding to the cytokines. *Id.* at \*11. She also noted that there was no evidence of any systemic cytokine activity on the day of the child's death. *Id.* Dr. McCusker testified that the cytokine production after a vaccine is controlled because cytokines do not have very long half-lives and are rapidly degraded by the system. *Id.* at \*11. Furthermore, Dr. McCusker called petitioners' theory "problematic" because the child was afebrile after the vaccination. *Id.* at \*12. She argued that if the cytokine production was such that it could affect the 5-HT system, it would have also produced a fever. *Id.*

Like the previous cases, the special master did not find that the Triple Risk Theory could reliably be extended to include vaccines or that cytokine activity is capable of impacting the brain's 5-HT system in the ways proposed by petitioners' experts. *See id.* at \*13–15.

#### **4. *Boatmon v. Sec'y of Health & Human Servs.***

Petitioners in *Boatmon* were initially successful in their claim, but there are many distinguishing factors between this case and the present one. *Boatmon*, 2017 WL 3432329. In that case, the child had a fever and was lethargic after vaccination. *Id.* at \*5. His parents administered Advil, but the fever returned the next day. *Id.* The child succumbed to SIDS later that afternoon following vaccination. *Id.* at \*6.

Drs. Miller and McCusker appeared in this case and largely presented the same arguments and medical literature from previous cases. In that case, however, the special master noted the "multi-factorial process" involved in SIDS and held that "petitioners ha[d] presented a reasonable and reliable theory of vaccine causation involving the role of inflammatory cytokines acting as an extrinsic stressor in a baby with a brainstem deficit during the vulnerable time period." *Id.* at \*38. The special master went on to quote Dr. Kinney and describe SIDS as "the biologic version of the perfect storm, in which the simultaneous and chance combination of multiple events is far more powerful than any individual event alone." *Id.*

Turning next to the applicability of the theory to the case facts, the special master found that despite the child's "entirely good health the day before[, o]vernight, he developed a mild fever, consistent with cytokine signaling from the vaccination site to the brain." *Id.* at \*39. Like most of the SIDS cases discussed, the special master found an appropriate temporal relationship existed between vaccination and SIDS. *Id.* at \*42. The special master ultimately held that petitioners had met their burden by a preponderance of the evidence and ruled in their favor. *Id.*

This decision was reviewed by the United States Court of Federal Claims and reversed. *See Boatmon v. Sec’y of Health and Human Servs.*, 138 Fed. Cl. 566 (Fed. Cl. 2018). The Court noted that “the Special Master dismissed as unlikely other possible external stressors” and “made no acknowledgment of the other cases reaching opposite conclusions[.]” *Id.* at 570–71. The Court went on to note that Dr. McCusker was the same expert used in *Boatmon* as in previous cases, and she was found to be a “‘superb witness’ and better qualified to discuss cytokines because of her cytokine research [and] her expertise in immunology[.]” *Id.* at 571. Finally, the Court was troubled by the fact that Dr. Kinney herself has not extended the Triple Risk Theory to vaccines, “nor has it been accepted by any other medical authorities outside those testifying in the Vaccine Program[.]” *Id.*

#### **D. Prong One**

A return to the question of “whether a vaccine-induced cytokine response is analogous to cytokine production post-infection” sharpens the application of *Althen* prong one to Dr. Miller’s theory of but-for causation of SIDS. In the *Boatmon* case where the special master initially found entitlement, this question was not explicitly answered. The special master noted that he “ha[d] not concluded that vaccines present a substantial risk to SIDS.” *Boatmon*, 2017 WL 3432329, at \*42. Instead, he focused on a “convergence of these factors [that] appears to be far more powerful than any one taken individually[.]” and found that the “role of inflammatory cytokines as neuro-modulators in the infant medulla . . . is likely the reason for a significant number of SIDS deaths occurring in conjunction with mild infection.” *Id.*

Petitioners’ theory previously appeared in *Jewell* and the expert opinions are similar. Ultimately, the theory that Petitioners present in this case fails for the same reasons articulated in *Jewell*. Due to the rare occurrence rate of many of the injuries that are examined in the Vaccine Program, it is often difficult, if not impossible, to find relevant studies to prove or disprove vaccine causation. Consequently, this type of evidence is not required to bring a successful claim. However, to the extent that studies do exist, they can be used to support or rebut a theory that a petitioner presents. In this case, Dr. Miller does not deny the existence of studies; rather, he attacks them stating, “none of the epidemiological studies on [the relationship between vaccines and SIDS] have been appropriately done[.]” Pet’rs’ Ex. 12 at 5.

Also, in the spirit of the Program, “to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation [P]rogram.” *Knudsen*, 35 F.3d at 549. A petitioner is tasked, however, with presenting a “sequence of cause and effect [that] is logical and legally probable[.]” *Id.* at 548–49 (internal citations omitted). In other words, to the extent that a petitioner does present a specific biological mechanism, it must be logical. Here, Dr. Miller’s theory was specific in its identification of a necessary brain vulnerability, its identification of stressors that are relevant to an infant’s susceptibility to SIDS, including vaccination, its identification of specific types of cytokines that are produced after vaccination, the effect of those cytokines on the body in the periphery, the mechanism for how said cytokines arrive in the brain, and the effect of those cytokines on the part of the brain suffering from the defect. For this sequence to compose a successful theory, all these pieces must work together even if it is not quite understood how. Indeed, the increase in cytokine

production levels must directly lead to the failure to rouse and the infant's subsequent death. This is where the theory fails.

Dr. McCusker relied on her in-depth knowledge of cytokines, including their perpetual presence in the brain and effects on all parts of the body, to explain why this sequence of cause and effect is illogical. Dr. McCusker agreed with Dr. Miller's explanation of SIDS and conceded the probability that a brainstem defect is present in most SIDS cases. She also discussed the relevant intrinsic risk factors and several exogenous factors to establish her knowledge of SIDS research. Dr. McCusker's focus, however, was on the nature of cytokine production and expression. Her explanation that infections produce a systemic response in the body whereas vaccines produce a more localized response was logical and uncontested. She then explained that cytokines have an extremely short half-life and would need an active transport system to enter the brain for a very specific purpose. Petitioners presented no evidence of such an active transport system, but Dr. Miller testified generally about the ways that cytokines can get into the brain. Ultimately, he stated that "[w]e don't know a whole lot about that system, but we do know that it's not distributed everywhere, . . . and it probably is somewhat selective so that different places in the brain have receptors and pumps for different cytokines." Tr. at 114:2-7. Dr. Miller did not tie a transportation mechanism to the cytokines produced locally after vaccination, and it remains unclear how or why they would arbitrarily find their way crossing the blood-brain barrier.

More importantly, Dr. McCusker persuasively rebutted Dr. Miller by explaining that cytokines need a normal brainstem to affect the 5-HT system because it is through functioning receptors that their messages are received. Dr. McCusker explained that the up-regulation of a specific cytokine can only affect the brain if the corresponding signal transducer is also up-regulated and neuronal transmission occurs. In the main study cited by Dr. Miller to make his point, the authors note that gp130 is the necessary component for expression of IL-6 and that it was not present in corresponding levels to IL-6 in SIDS patients. That supports Dr. McCusker's contention that IL-6 is not properly expressed in these infants and the brain does not even register the presence of these 'extra' cytokines. The logical conclusion would be that when a CO<sub>2</sub>-inducing event occurs in a vulnerable infant, whether it be increased metabolism from infection or prone sleeping, the presence or lack of cytokines is inconsequential because they cannot express without gp130. The ultimate cause of death is the cause of the increased CO<sub>2</sub> that leads to the cessation of breathing and not the cytokines' effect on the arousal system. The cytokines may in fact be a marker of this inability to breathe, or a potential mechanism for arousal. However, the evidence suggests that the cytokines do not express because of the lack of gp130, and there is no evidence that this failure to up-regulate is linked to vaccination. There is also no link between the vaccination and the initial process by which the infant stops breathing. Dr. McCusker walked through Dr. Miller's theory and identified these areas where the logic fails based on what is known about cytokine expression.

It should be recognized, as Petitioners noted, that Dr. McCusker can, at times, overstate her position, particularly as it relates to providing support to some of her conclusions. Dr. McCusker's addition of the loosely tucked sheet as a risk factor based on literature that discourages "soft materials or objects such as pillows, quilts . . . placed under a sleeping infant" is one example of overreach. Dr. McCusker also asserted that several studies have shown "increased CO<sub>2</sub> associated with [URI]s in infants[.]" Tr. 274:15-17. However, under cross-examination, she was

unable to identify any such study and instead stated that it was “basic pediatrics” that “is generally accepted.” Tr. 274:17–21. Ultimately, Dr. McCusker admitted “there is no study that measures CO2 levels in SIDS patients.” Tr. 275:9–10. Dr. McCusker undercuts her impressive credentials with unnecessary overreach. Despite these exchanges, Dr. McCusker provided logical explanations for why Dr. Miller’s theory cannot work as articulated. Dr. Miller, while certainly knowledgeable in the field of pathology, did not have a response for many of her criticisms regarding his explanation of cytokine expression. Consequently, his theory fails.

#### **E. Prong Two**

Without a logical and legally probable theory that meets the preponderant standard, it is difficult to analyze the facts of this case pursuant to prong two of *Althen*. Petitioners and Respondent agree that it is more likely than not that J.J. was a vulnerable infant that succumbed to SIDS consistent with the Triple Risk Theory. The disagreement lies in the exogenous stressor that was the biological mechanism for J.J.’s death. Dr. Miller does not point to any evidence that J.J.’s immune system over-produced cytokines in response to vaccination. He does not point to evidence that any such cytokines were produced near the vaccination site but migrated to the CNS and crossed the blood-brain barrier. Finally, he does not point to any evidence in the medical record that J.J. suffered from a systemic immune response to vaccination similar to what one would expect if J.J. had an infection. The record does not contain evidence to show that it is more likely than not that Dr. Miller’s theory is illustrated by J.J.’s case.

#### **F. Prong Three**

Although Petitioners were unsuccessful with respect to *Althen* prongs one and two, the medical record clearly reflects that J.J. succumbed to SIDS less than 24 hours after vaccination. Petitioners’ causation theory does not provide an appropriate time frame for vaccine-caused SIDS. However, if Petitioners had been able prove their theory under the preponderant standard, the temporal relationship between vaccination and death would have, more likely than not, been appropriate given the proximity in time discussed with regard to infection-induced SIDS. The temporal relationship can support a theory for causation but is not alone sufficient to establish causation without additional persuasive evidence.

#### **V. Conclusion**

Petitioners’ claim fails because they did not establish by a preponderance of the evidence that vaccines can trigger an immune response analogous to infections in vulnerable infants as defined by the Triple Risk Theory, and that J.J.’s vaccinations did so, resulting in his death. This theory has been unsuccessfully litigated in the Program previously, and Dr. Miller did not present any new persuasive evidence.

The death of a child is an unimaginable loss, and the lack of information that medical professionals have to provide answers when such a tragedy occurs can exacerbate said loss. In an effort to understand what happened in this case and why, the medical record, expert reports, medical literature, and hearing testimony were all thoroughly reviewed and considered, even if not

explicitly referenced herein. Considering the totality of the record in this case, there is not sufficient evidence of vaccine but-for causation.

**Accordingly, the undersigned has no choice but to DENY Petitioners' claim and DISMISS this petition.**

**IT IS SO ORDERED.**

s/Herbrina D. Sanders  
Herbrina D. Sanders  
Special Master